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ADDISON'S DISEASE: EVALUATION OF SYNTHETIC DESOXYCORTICOSTERONE ACETATE THERAPY IN 158 PATIENTS*

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INTRODUCTION

THE immediate and favorable response of patients with Addison's disease to synthetic desoxycorticosterone acetate therapy is now well established.[1, 2, 3, 4, 5] The effect which treatment with desoxycorticosterone acetate will have on the life expectancy of patients with Addison's disease cannot be stated at this early date, although our experience indicates that there has been a considerable reduction in mortality rate during the first 18 months of therapy.

The present report summarizes our experience with synthetic desoxycorticosterone acetate therapy during the past three years. In this period 158 patients with classical signs and symptoms of Addison's disease have been treated with the synthetic hormone. Sixty-four patients have been under our direct observation in The Johns Hopkins Hospital, and 94 patients have been treated by physicians elsewhere. The majority of these patients (148) have received subcutaneous implantations of pellets of crystalline hormone * following a carefully conducted assay period in which the optimum daily maintenance dose of hormone was determined by means of a single daily intramuscular injection of hormone in oil (4 to 12 weeks).

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* In all instances we have used standardized sterile pellets of crystalline desoxycorticosterone acetate weighing approximately 125 mg., which were provided through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, N. J.

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In this report data relating to the age and sex of the patients, etiology of the disease, hormone requirement and mortality rate will be presented for the entire group of 158 patients. More detailed observations relating to the course of the disease during treatment, changes in body weight, blood pressure, blood chemistry, electrocardiogram and electroencephalogram will be limited to the group of 64 patients who were directly under our observation

TABLE I

Etiology of Addison's Disease in a Group of 158 Patients Treated with Desoxycorticosterone Acetate

	MALE		FEMALE		TOTAL	
	Total No. of Cases	Non-Tuberculous	Total No. of Cases	Non-Tuberculous	Number of Cases	Non-Tuberculous
Johns Hopkins Hospital	34	80%	30	77%	64	78%
Other Cases	55	37%	39	64%	94	48%
TOTAL	89	53%	69	70%	158	60%

in The Johns Hopkins Hospital. All cases of Addison's disease which have been reported previously by us [1, 2, 5] are included in the present report.

Etiology of the Disease: For convenience the etiological factors responsible for the adrenal cortical insufficiency in this group of patients have been classified as *tuberculous* or *non-tuberculous* (table 1). There appears to be a much lower incidence of tuberculosis of the adrenals in this group (40 per cent on the basis of clinical and laboratory diagnosis; 50 per cent on the basis of the 14 autopsy records) than has been observed previously (table 2). Conybeare and Millis [6] noted an incidence of 76 per cent of tuberculosis

TABLE II

Etiology of Addison's Disease—Postmortem Studies (Patients Treated with Desoxycorticosterone Acetate)

Patient	Age	Sex	Classification (Clinical and Lab. Studies)	Postmortem Findings—Adrenals
J. B.	52	M	Tuberculous	Tuberculosis
M. B.	31	F	Non-Tuberculous	Atrophy
R. B.	45	F	Non-Tuberculous	Atrophy
A. K.	30	F	Non-Tuberculous	Atrophy
J. L.	41	M	Tuberculous	Tuberculosis
A. M.	48	M	Tuberculous	Tuberculosis
G. M.	32	F	Non-Tuberculous	Atrophy
M. M.	27	F	Non-Tuberculous	Atrophy
S. M.	50	M	Tuberculous	Tuberculosis
S. O.	30	M	Tuberculous	Tuberculosis
O. Q.	62	M	Non-Tuberculous	Atrophy
D. R.	27	F	Non-Tuberculous	Atrophy
F. S.	28	M	Tuberculous	Tuberculosis
I. T.	69	F	Tuberculous	Tuberculosis

SUMMARY:
Tuberculous —7
Non-Tuberculous—7

of the adrenals in a series of 29 autopsies and Rowntree and Snell [7] report 84 per cent in a group of 31 cases (autopsy records) of Addison's disease.

Age and Sex: Approximately 80 per cent of the total number of cases in this series occurred in patients 20 to 50 years of age (table 3). The average

TABLE III

Age and Sex of Patients with Addison's Disease Treated with Desoxycorticosterone Acetate

Age	Males	Females	Total
0–10	0	0	0
10–20	7	3	10
20–30	20	12	32
30–40	24	22	46
40–50	26	21	47
50–60	7	9	16
60–70	5	1	6
70–80	0	1	1
TOTAL	89 (56%)	69 (44%)	158

age of the male patients was 37.2 years and the average age of the female patients was 40.0 years, the average for the entire group of 158 patients being 38.4 years. A comparison between the number of patients in this age group and the general population (chart 1) indicates that the apparent in-

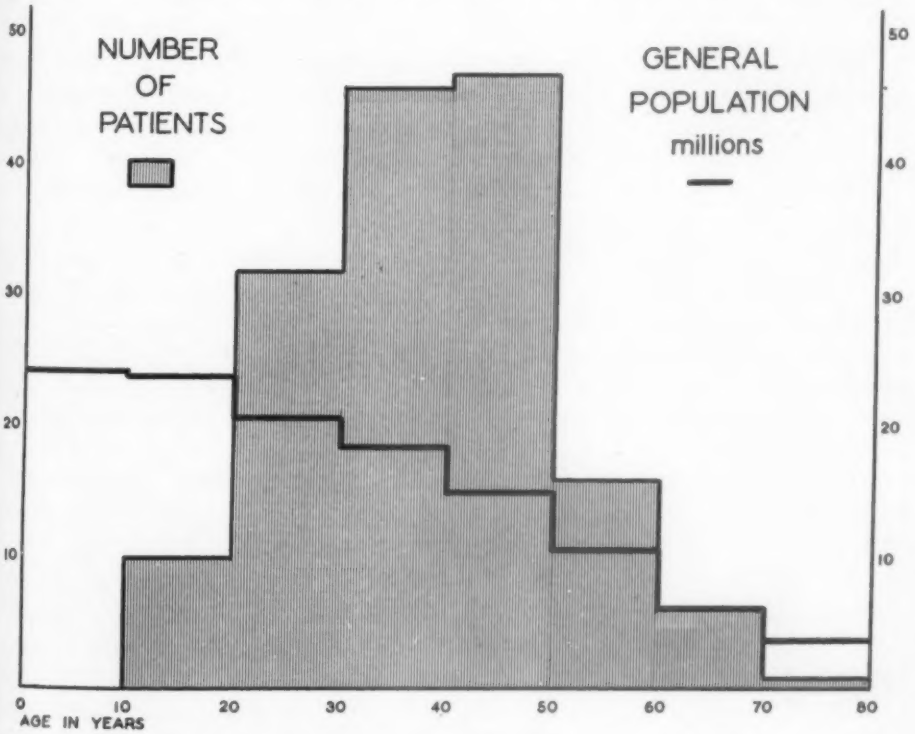

CHART 1. Age of patients with Addison's disease (158 cases).

creased incidence of Addison's disease in this age group is real. Although the number of males predominated (table 3), the difference in incidence between the sexes was not great.

Symptomatology: An analysis of the presenting symptoms in the 64 patients with Addison's disease who were seen in The Johns Hopkins Hospital is recorded in table 4. Weakness, fatigability, increasing pigmentation, anorexia and nausea were present in most instances. Ten patients (16 per cent) noted a definitely increased desire for salt and salty foods. A similar increase in "salt appetite" has been noted in adrenalectomized rats.[8]

TABLE IV

Analysis of Symptoms in 64 Patients with Addison's Disease

	Number	Per Cent
Weakness and fatigability	64	100
Increasing pigmentation	60	94
Anorexia	58	91
Nausea	55	86
Vomiting	48	75
Constipation	21	33
Abdominal pain	20	31
Diarrhea	10	16
Salt craving	10	16
Muscle pain	8	13

Diagnosis: From the group of 64 patients reported from The Johns Hopkins Hospital we have excluded all in whom there was the slightest doubt regarding the diagnosis of Addison's disease. Fifty-eight of the 64 patients had been seen at some time in typical adrenal crisis. The diagnosis in the other four patients was substantiated by careful clinical observations over a period of years. In the 94 patients who were not under our direct care we have relied upon the diagnosis of Addison's disease as established by the attending physician. In most instances these patients have also been seen in adrenal crisis and have, in addition, exhibited the changes characteristic of the syndrome, i.e., increasing pigmentation, hypotension, weakness, weight loss, anorexia and hypochloremia. The diagnosis of Addison's disease was substantiated in each instance in which a postmortem examination was made.

Desoxycorticosterone Acetate Therapy: In most patients treatment with desoxycorticosterone acetate was initiated by administering a daily intramuscular injection of the synthetic hormone in sesame oil (Percorten, Ciba; 1 c.c. contains 5 mg. of hormone) with or without supplementary sodium chloride therapy. The majority of patients required 5 mg. or less of Percorten daily (table 5) with 4 gm. (average) of supplementary sodium chloride medication. Less than 10 per cent of the patients required more than 5 mg. of hormone daily. The initial dose of hormone was usually much greater than the ultimate maintenance dose, since most patients were in rather

poor condition at the time synthetic hormone therapy was instituted. As their condition subsequently improved under desoxycorticosterone acetate treatment, the hormone requirement decreased considerably. However, it often required several weeks before the minimum maintenance dose was attained.

Although supplementary sodium chloride therapy was not required in order to obtain successful regulation with the synthetic hormone,[2] it was used in most instances because it greatly reduced the hormone requirement and hence the cost of therapy. For most patients this was a consideration

TABLE V

Daily Maintenance Dose of Desoxycorticosterone Acetate in Sesame Oil of 141* Patients with Addison's Disease

Daily Dose of Hormone mg.	Number of Patients
0–1	0
1–2	53
2–3	20
3–4	8
4–5	48
5–10	8
10+	4
3.8 mg. per day, average	141 patients

* Assays in 17 patients were not standardized sufficiently to warrant inclusion in this table.

which could not be neglected. However, at present, 60 patients are being maintained with pellets of synthetic hormone *without* supplementary sodium chloride therapy. Supplementary sodium chloride therapy was best tolerated when given in the form of *1 gm. enteric coated tablets, at meal time with food,* a total of 3–5 gm. per day being the quantity most frequently used. It is undesirable to administer more than 5 gm. of supplementary sodium chloride therapy daily to most patients, even though well tolerated, since the onset of an acute infection or gastrointestinal disorder is usually accompanied by an inability to take the sodium chloride tablets and hence the patient is suddenly deprived of a large part of his therapy at a time when his need is greatest. A supplement of 3 gm. of sodium chloride daily was always used when patients were being prepared for pellet implantation (vide infra). Sodium chloride therapy in conjunction with desoxycorticosterone acetate treatment is *contraindicated* in patients who are predisposed to edema formation, hypertension or circulatory insufficiency.

The desirability of implanting pellets of crystalline hormone was considered after a patient had been maintained in good condition for a period of one month or more with daily injections of Percorten (crystalline hormone in sesame oil). Pellets were implanted in 148 of the patients in this group (table 6) after careful clinical control had permitted the daily requirement of hormone in oil to be determined accurately (table 5). In most instances it re-

quired at least four weeks to determine the optimum maintenance dose of hormone.

Calculation of Pellet Requirement: The number of pellets (Ciba; 125 mg. each) to be implanted was calculated directly from the daily maintenance dose of hormone in oil, injected intramuscularly. One pellet of 125 mg.* was implanted for each 0.5 mg. of hormone so required by daily injection.

TABLE VI

Initial Pellet Requirement of Patients with Addison's Disease

Number of Patients	Average Number of Pellets of Crystalline Desoxycorticosterone Acetate †	Total Quantity of Hormone per Patient (Aver.)
148*	6.4 (Range 2–15)	820 mg. (Range 250–1875)

* 10 patients have been treated with intramuscular injections of hormone in oil (Percorten) only.

† Pellets weighed 125 mg. ± 6 mg.

A small constant quantity of supplementary sodium chloride medication (3 gm. daily) was administered during the period of assay. This provided a balancing mechanism which could be used after pellets were implanted to compensate for any temporary excess of hormone. Thus, in the event that excessive sodium chloride was retained (edema) following pellet implantation it was possible to correct this by discontinuing a part or all of the added sodium chloride medication. If necessary, sodium chloride in the diet could also be restricted. Maintaining the sodium chloride therapy at a low dosage level (3 gm. daily) permitted an appreciable increase in the quantity of supplementary sodium chloride at a later date, should this be desirable. In this way a temporary need for additional therapy might easily be met by increasing the quantity of sodium chloride therapy. This could not have been done had the patient been receiving large doses of sodium chloride.

Pellets, weighing 125 mg. each, provided effective therapy in most patients for a period of at least 12 months. The fact that pellets were no longer providing an adequate supply of hormone was first indicated in most instances by a gradual reduction in blood pressure. Later fatigue, loss of weight and appetite were observed. However, in most instances, as soon as the reduction in blood pressure was noted, without awaiting the further development of symptoms of adrenal insufficiency, the patient was given intramuscular injections of hormone. One injection of 2 to 5 mg. (0.4 to 1.0 c.c.) of Percorten, twice weekly, was adequate for most patients at this

* Standardized pellets of desoxycorticosterone acetate prepared by Ciba Pharmaceutical Products, Inc., Summit, N. J., were used throughout these studies. The rate of absorption of these pellets has been shown to be 0.3 to 0.5 mg. per day per pellet. Pellets prepared in a different manner with a different rate of absorption should not be implanted on the basis of the calculation used in these studies, i.e., 1 pellet of 125 mg. for each 0.5 mg. of hormone required by daily injection.

time. Later daily injections of the hormone were resumed and a new assay was conducted. Three grams of sodium chloride daily were administered during this new assay period. When the maintenance hormone requirement had again been ascertained, and when it was certain that little, if any, of the original pellets remained, new pellets were implanted. *New pellets of desoxycorticosterone were never implanted arbitrarily at the end of one year, on the basis of the original assay* for two reasons: first, patients' hormone requirement often changed considerably after a year of sustained therapy; secondly, in many patients at the end of 12 months, there was still an appreciable quantity of hormone which was being absorbed from the original pellets and which would have led to overdosage if supplemented by a full complement of new pellets. At present 61 of the patients have received two or more implantations (table 7). The average duration of time which

TABLE VII

Number of Implantations of Pellets of Crystalline Desoxycorticosterone Acetate

Number of Implantations	Number of Patients
1	148
2	61
3	12
4	1
Total Number of Implantations	222

elapsed between the first and second implantations was 12.3 months. In most patients supplementary injections of hormone in oil were not required during the first 12 months subsequent to the initial pellet implantation.

Technic of Pellet Implantation: The infrascapular region posteriorly was selected for pellet implantation. Strict asepsis was observed. The operative field was prepared with iodine and alcohol and the site of incision was infiltrated with procaine, 1:200 solution. A transverse incision 2 to 4 cm. in length was made a few centimeters below the inferior spine of the scapula. With blunt dissection a number of small pockets, 2 to 3 cm. in depth were prepared in the subcutaneous tissues. The opening of each pocket was held far enough apart by a nasal dilator to permit pellets to be dropped gently to the bottom of the pocket without the use of force. This was important, for if the opening into the pocket were too small the fragile pellet could easily be crushed by the force used to insert it; furthermore, if the pocket were not deep enough, the pellet might be extruded subsequently through the incision. The wounds were closed with subcuticular stitches of fine black silk. It was possible to insert as many as 10 to 15 pellets through a single incision.[5]

At present 131 of the 132 patients now alive are being treated with pellets of hormone. Of this number 60 are receiving *no supplementary sodium chloride medication* at present. Six patients in addition to desoxycorti-

costerone acetate treatment are receiving 3 to 6 c.c. daily of adrenal cortex extract (Wilson, Upjohn or Parke, Davis & Co.). Supplementary injections of synthetic hormone in oil (Percorten, Ciba), intravenous administration of saline and glucose solutions and large doses of adrenal cortex extract, 5 to 10 c.c. at 4 to 8 hour intervals have been administered to many of these patients during the course of acute infections or in preparation for operative procedures.

The sublingual administration of desoxycorticosterone acetate in propylene glycol according to the method of Anderson et al.[9] has been tested in five patients with Addison's disease.[10] It was shown that this method was effective, but not efficient (table 8). It appears that administration of hormone sublingually may be useful in the treatment of patients whose hormone requirement is small and who are able to afford the increased quantity of hormone required by this route of administration. Recently we have tested solid tablets of crystalline desoxycorticosterone acetate "Linguets"* for sublingual administration and have found them very much more convenient to administer than the hormone in propylene glycol although the tablets are no more efficient than hormone in propylene glycol administered sublingually. The results obtained on a comparative assay of "Linguets" and Percorten are presented in chart 2. Patients receiving desoxycorticosterone acetate sublingually are not immune from the complications which have been reported in patients treated with intramuscular injections or subcutaneous implants of hormone. In patient M. D. edema readily developed when the dose of hormone, administered in propylene glycol sublingually, was increased above the minimum maintenance dose.

TABLE VIII

Relative Effectiveness of Desoxycorticosterone Acetate Administered Subcutaneously (Pellets), Intramuscularly, and Sublingually

	Equivalents
Subcutaneous implantation of pellets of crystalline hormone	1.2 mg. daily
Intramuscular injection of hormone in oil (once daily)	2.0 mg. daily
Sublingual administration of	
(*a*) Desoxycorticosterone acetate in propylene glycol	6.0–8.0 mg. daily
(*b*) Solid tablets of crystalline hormone in glucose	6.0–8.0 mg. daily

Results of Therapy: The mortality rate for the entire group of 158 patients was 15.4 per cent for a period of 1.7 years of therapy, or an annual mortality rate of 9.2 per cent, per year (table 9). A comparison with earlier reports on the life expectancy of patients with Addison's disease before the

* Tablets ("Linguets") composed of desoxycorticosterone acetate (1, 2, 5 and 10 mg. respectively), lactose, sucrose, talcum and gum arabic for sublingual use were prepared by Ciba Pharmaceutical Products, Inc.

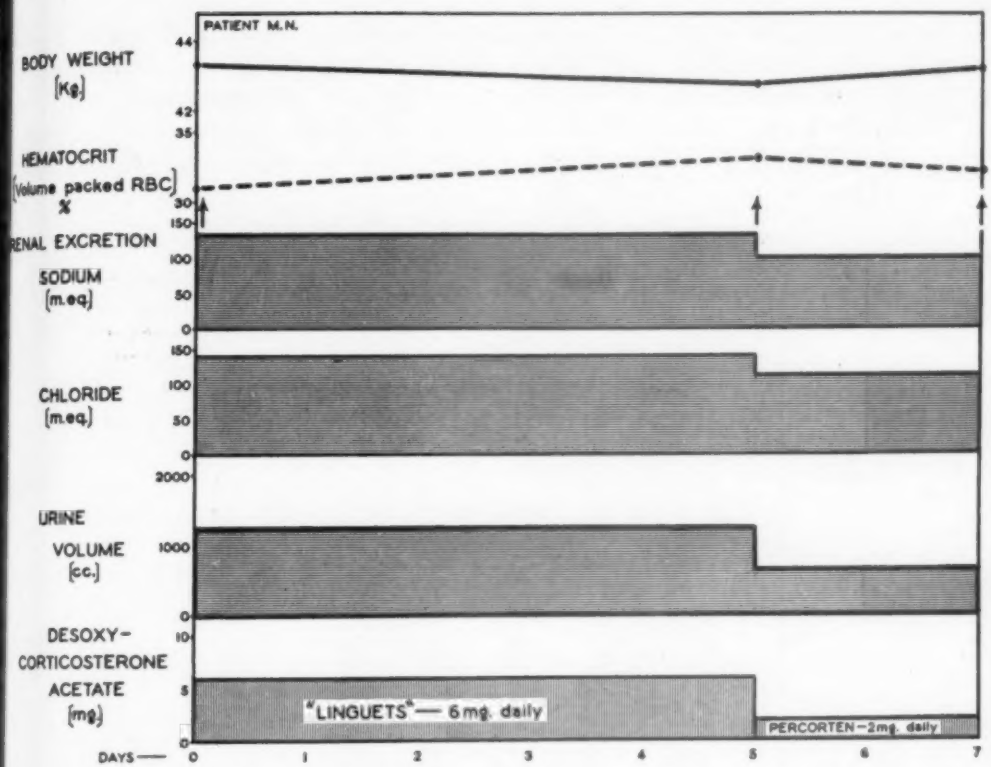

CHART 2. The relative effectiveness of desoxycorticosterone acetate tablets ("linguets") for sublingual use and a single daily injection of synthetic hormone in oil ("percorten").

TABLE IX

Mortality Rate in 158 Patients with Addison's Disease Treated with Desoxycorticosterone Acetate

	Number of Patients	Duration of Therapy	Number of Deaths	Mortality Rate
Johns Hopkins Hospital...	64	1.8 yr.	10	16.0%
Other Cases.....	94	1.6 yr.	14	14.9%
TOTAL.....	158	1.7 yr.	24	15.2%

era of specific therapy and during the period of extract and sodium chloride therapy has been made (chart 3). The possible rôle played by added sodium chloride therapy in the present series of cases is controlled by the mortality rate which was observed when combined extract and sodium chloride therapy were employed (44.2 per cent at the end of 1.5 years). In regard to the group treated with adrenal cortex extract it is only fair to state that in all likelihood these patients did not, for the most part, receive adequate hormone therapy. There is no doubt, however, that they received all of the sodium chloride medication which they could tolerate. Thus, the mortality rate for

this group more correctly represents the mortality rate for a group of patients who received adequate sodium chloride therapy, but, for the most part, inadequate extract therapy. The reasons for the latter were, and still remain, the high cost of adrenal cortex extract therapy and the necessity for frequent injections of this hormone preparation if the best clinical results are to be obtained.

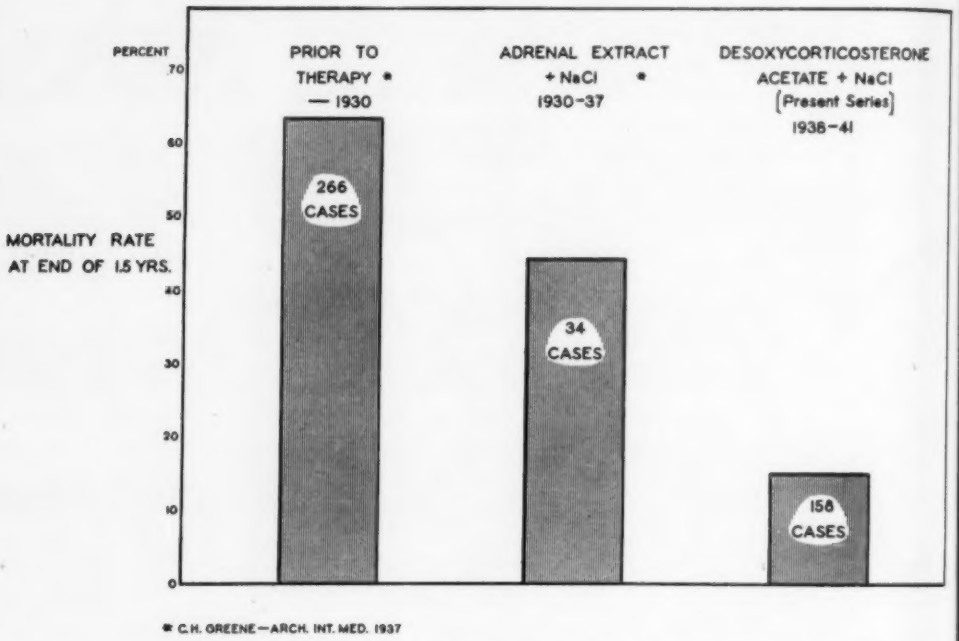

CHART 3. Comparative mortality rates in patients with Addison's disease prior to and subsequent to use of specific therapy.

Not only was the mortality rate greatly reduced in the group of patients treated with desoxycorticosterone acetate but the clinical improvement in the majority of patients was very striking. At this point it may be of interest to quote from Rowntree[7] who stated prior to the use of specific hormone therapy: "Most patients with Addison's disease are invalids throughout the course of the disease. Not more than one patient out of four or five is rehabilitated even to 50 per cent of former working capacity for as long as one year, and not more than one in sixty is rehabilitated to the extent of 75 to 80 per cent of previous working capacity for five years. None of the patients in our series has been completely restored to health and normal strength." In the group of 64 patients studied in the Johns Hopkins Hospital there occurred an average gain of approximately 4 kg. during the 1.7 years of therapy (chart 4). There was also a corresponding rise in blood pressure from an average level of 100 mm. Hg systolic and 66 mm. diastolic prior to therapy to a level of 126 mm. Hg systolic and 76 mm. diastolic at present.

Statistical analysis of these data indicates that the changes in all instances are significant.* The factor for difference between means is 4.9 in respect to the values for body weight, 6.3 for systolic blood pressure values, and 6.5 for diastolic pressure values.

A total of 31 of the 64 patients in our group improved so markedly during desoxycorticosterone acetate treatment that they were fully rehabilitated

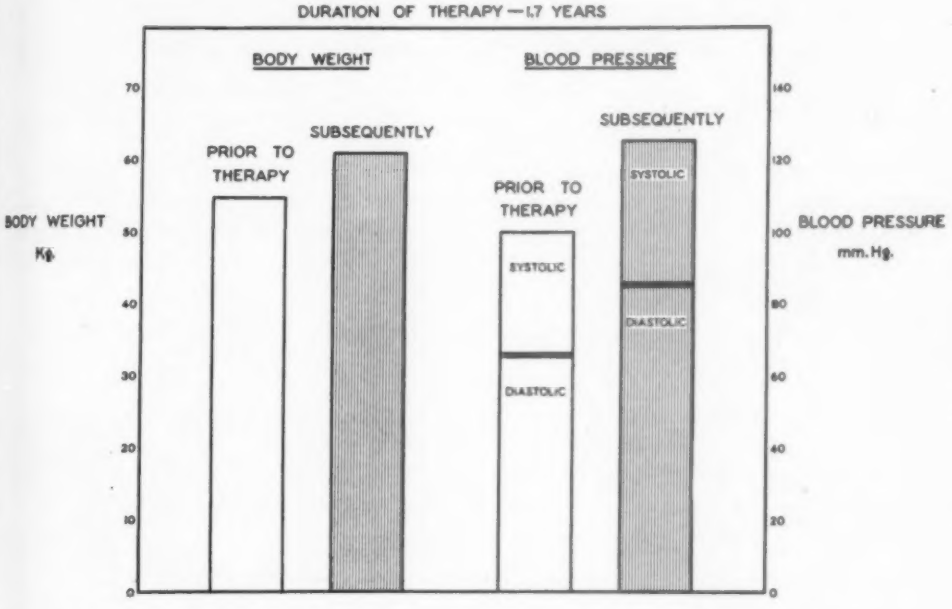

CHART 4. Effect of desoxycorticosterone acetate therapy in Addison's disease (Johns Hopkins Hospital—64 patients).

(table 10). Nineteen of these 31 patients were males. All 19 of these male patients are employed *full time* at present (table 11). Sixteen patients (25 per cent) have been greatly improved by therapy but cannot be considered to have been restored completely to normal strength and activity; in five of these 16 patients there is a complicating disease which will prevent these patients from returning completely to normal health (table 10, footnote 2). Seven patients in the group of 64 have shown little or no improvement. In four of these patients there is a definite complication (table 10, footnote 3); in the remaining three there is no apparent reason for the failure of desoxycorticosterone acetate therapy. The therapeutic results which were achieved in the outside group of patients (94) approximated closely the results which were obtained in the Johns Hopkins Hospital group.

* The difference between means is significant when the value of this factor is greater than 2.

See footnote to table 22.

TABLE X

Summary of Present Status of 64 * Patients with Addison's Disease (Johns Hopkins Hospital) Treated with Desoxycorticosterone Acetate

	Number	Per Cent	
Striking improvement (fully rehabilitated)	31	48	75
Improved—but not fully rehabilitated†	17	27	
No improvement‡	6	9	
Deaths	10	16	

* 62 of these patients have been treated with subcutaneously implanted pellets.

† This group includes 3 patients with tuberculosis and 2 patients with rheumatic heart disease.

‡ This group includes 1 patient with tuberculosis; 1 patient with coronary infarction; 1 patient with marked hypertension which antedated onset of Addison's disease.

The immediate causes of death in the 10 patients in the Hopkins group and in the 14 patients in the outside group have been listed in table 12. Acute intercurrent infections and cardiovascular accidents account for more than 50 per cent of the deaths. These complications will be considered in some detail later. The two patients who died from hypoglycemia represent, in our estimate, preventable deaths, if preparations with "carbohydrate-regulating" potency had been used. In neither instance was the patient able to afford supplementary extract therapy.

TABLE XI

Effect of Desoxycorticosterone Acetate Therapy on Rehabilitation of Male Patients with Addison's Disease (Johns Hopkins Hospital)

Total Number of Male Patients	Number now Employed Full time	Per Cent
34	19	56%

In addition to the disturbance in carbohydrate metabolism which persisted in patients adequately treated with desoxycorticosterone acetate certain other signs and symptoms of adrenal insufficiency also failed to respond to continued hormone therapy in a small proportion of the patients. Thus, four patients (approximately 6 per cent of the Johns Hopkins Hospital

TABLE XII

Immediate Causes of Death in 24 Patients with Addison's Disease (Entire Group of 158 Patients)

	Number	Per Cent
Acute intercurrent infections	7	29
Cardiovascular disease	7	29
Tuberculosis	4	17
Hypoglycemia	2	8
Discontinued therapy	1	4
Unexplained	3	13
TOTAL	24	

group) lost weight during a prolonged period of desoxycorticosterone acetate treatment (2.5 years, average duration of treatment). In six of the patients (approximately 10 per cent) an appreciable degree of muscular weakness and asthenia persisted. In three patients (approximately 5 per cent) anorexia, nausea, and occasionally vomiting were observed.

Disturbances in Carbohydrate Metabolism: Recent studies [11] have increased our understanding of the nature of the disorder in carbohydrate metabolism which occurs in patients with Addison's disease. It now appears that any or all of the following defects may be observed in these patients:

1. Decreased rate of absorption of glucose from the gastrointestinal tract (flat glucose curve).
2. Increased utilization of carbohydrate.
3. Impaired ability to form new carbohydrate from non-glucose sources, i.e., "impaired gluconeogenesis."
4. "2" and "3" facilitate depletion of liver glycogen reserves and consequently predispose to hypoglycemia.
5. Lowered threshold at which signs and symptoms of hypoglycemia become evident.

Patients with Addison's disease vary widely in the extent to which disturbances in carbohydrate metabolism complicate their illness. Some patients develop hypoglycemia only during the course of intercurrent infections, prolonged fasting, or other stresses, whereas other patients have been known to display signs and symptoms of hypoglycemia after a brief postponement of a meal. To detect underlying disturbances in carbohydrate metabolism we have tested 52 of our patients with an intravenous glucose tolerance test * in which the development of moderate or severe signs and symptoms of *hypoglycemia* two to three hours after the intravenous administration of glucose signifies the presence of a rather profound disturbance in carbohydrate metabolism.[11] Of the group of 52 patients tested, 39 developed marked signs and symptoms of hypoglycemia two to three hours after the glucose solution had been injected intravenously (table 13). Twenty-six of these 39 patients had experienced similar episodes of hypoglycemia spontaneously. In 13 of the patients the positive reaction to this test constituted the first clinical evidence of a disturbance in carbohydrate metabolism. Thirteen patients in the group of 52 gave no evidence of the existence of any disturbance in carbohydrate metabolism by this test, and no history of spontaneous hypoglycemic episodes.

* *Standard Intravenous Glucose Tolerance Test.* Glucose, 0.5 gm. per kg. body weight, is injected intravenously as a 20 per cent solution in *distilled water.* The rate of flow is so adjusted that the infusion is completed in 30 minutes. Capillary blood for sugar determinations is taken in the fasting state and at 30 minute intervals for three to four hours following the completion of the infusion. Urine specimens are collected at appropriate intervals and analyzed for sugar.

It is of interest to note that restoration of plasma volume, plasma electrolyte concentration and blood pressure to normal levels by means of desoxycorticosterone acetate therapy does not correct the underlying disturbance in carbohydrate metabolism.[11] Only the gastrointestinal absorption of glucose is facilitated by synthetic hormone therapy, whereas treatment with adrenal cortex extract (large doses [50 c.c.] by injection) or certain, naturally occurring, crystalline adrenal steroid compounds (corticosterone, dehydrocorticosterone, 17-hydroxy-dehydrocorticosterone) promotes gluconeogenesis, depresses glucose utilization, increases liver glycogen stores

TABLE XIII

Incidence of Abnormal Carbohydrate Metabolism in 52 Patients with Addison's Disease (Johns Hopkins Hospital)

	Number of Patients	Per Cent
Spontaneous hypoglycemia	26	50
Hypoglycemia induced by intravenous glucose tolerance test	39	75
No evidence of disturbance in carbohydrate metabolism	13	25

and raises blood sugar levels.[11, 12] Unfortunately adrenal steroids with "carbohydrate-regulating" potency are not as yet available for clinical use, and adrenal cortical extract in quantity sufficient to affect carbohydrate metabolism significantly cannot be afforded by most patients. Thus, with the exception of the use of adrenal cortex extract therapy in patients in crisis, the treatment of hypoglycemia consists primarily in attempting to prevent its occurrence by the use of frequent feedings of a diet high in readily available carbohydrate content.

Treatment of Adrenal Crisis: In most instances intercurrent infections were responsible for the precipitation of adrenal crises in patients treated with desoxycorticosterone acetate. In a few patients the development of hypoglycemia, spontaneously, acted as the exciting factor. Of all infections, those due to streptococcus appeared to be the most frequent and most severe. Because of the rapidity with which crisis is precipitated during the onset of acute respiratory infections, treatment must be instituted immediately, if possible. The use of sulfadiazine is of great aid in the treatment of streptococcus infections in patients with Addison's disease.[13]

The aims of therapy in patients in crisis or in impending crisis may be summarized as follows:

1. Support of plasma volume and blood pressure by

(*a*) Intravenous infusion of sodium chloride (0.9 per cent solution) and dextrose (5 to 10 per cent solution).

(*b*) Aqueous adrenal cortex extract (intravenously and subcutaneously) in large quantities.

(*c*) Synthetic desoxycorticosterone acetate in oil (intramuscularly) to supplement maintenance dose.
(*d*) Epinephrine in oil (0.5 c.c.) intramuscularly if systolic blood pressure falls below 90 mm. Hg.

2. Prevention of hypoglycemia.

(*a*) Infusions of dextrose (see 1 *a*).
(*b*) Frequent feedings of readily available carbohydrate as soon as tolerated
(*c*) Large quantities of adrenal cortex extract (1 *b*).

3. Antibacterial chemotherapy whenever indicated.

4. Plasma and whole blood transfusions are not recommended as routine procedures.

Suggested Outline of Therapy: 1. The patient is placed in a warm bed with adequate blankets and *is immediately given an intravenous infusion of 1,000 to 1,500 c.c. of sodium chloride 0.9 per cent and glucose 5 to 10 per cent.* This is repeated in 12 hours and is given subsequently at least once daily until the temperature has reached normal or until the patient is taking fluids and eating well.

2. Twenty-five c.c. of aqueous adrenal cortex extract are added to the infusion and in addition 10 c.c. of extract are injected subcutaneously. The subcutaneous injection of 5–10 c.c. of aqueous extract (Wilson, Upjohn or Parke, Davis) is repeated every two to four hours until fever subsides, then every four to eight hours until the patient is eating well.

3. Twenty milligrams of desoxycorticosterone acetate in oil are injected intramuscularly in divided doses immediately; and thereafter 5 to 10 mg. are given once daily depending upon blood pressure, quantity of saline solution which has been administered, appearance of excessive fluid retention, etc.

4. One c.c. of epinephrine in oil injected intramuscularly is indicated if the level of systolic blood pressure falls below 90 mm. Hg.

5. Blood pressure determinations are made at intervals of one to two hours, day and night. Small quantities of fruit juice with added lactose, or ginger ale, are given at frequent intervals if tolerated. Since 1,500 c.c. of saline and dextrose solution are given intravenously at 8 to 12 hour intervals, additional fluid or sodium chloride by mouth is not essential during the first 24 hours of treatment. A fall in blood pressure without signs of excessive sodium chloride and water retention is a definite indication for increasing the infusions of sodium chloride and for giving additional desoxycorticosterone acetate intramuscularly (5 to 10 mg.). A fall in blood pressure in the presence of excessive sodium chloride and water retention is a definite indication for reducing the number of infusions, for discontinuing the desoxycorticosterone acetate therapy and for *increasing* the quantity of adrenal cortex extract, i.e., 10 c.c. every hour. *At this time a plasma transfusion*

should be seriously considered. Our experience with the unfavorable reaction of patients with Addison's disease to whole blood transfusions suggests that this therapeutic procedure should be withheld unless other measures fail.

As a precautionary measure we urge that all patients with Addison's disease keep on hand *at all times or have immediate access to the following:*

Emergency Kit:

1. 1000 c.c. of 0.9 per cent NaCl and 5 to 10 per cent glucose solution for intravenous administration.
2. Sulfadiazine tablets.
3. Adrenal cortex extract, *50 c.c.* (Wilson, Upjohn, Parke-Davis).
4. Synthetic desoxycorticosterone acetate in oil, 10 c.c. (Percorten, Ciba; Cortate, Schering; Doca, Hoffmann-LaRoche).

Complications Which May Arise During Desoxycorticosterone Acetate Therapy.

1. *Non-specific:* Hypoglycemia occurs not infrequently in patients treated with desoxycorticosterone acetate alone. This complication has already been referred to (see "Disturbances in carbohydrate metabolism"). Treatment consists in frequent feedings of a diet high in readily available carbohydrate and supplementary injections of aqueous adrenal cortex extract, 5 to 10 c.c. every four to six hours.

In two patients intramuscular injections of desoxycorticosterone acetate in sesame oil (Percorten) were accompanied by localized redness, pain and tenderness at the site of the injection, as well as fever and malaise. It was demonstrated subsequently that these reactions were due to the injection of sesame oil and not to synthetic hormone.[5] Both patients did well when pellets of crystalline hormone were implanted.

On four occasions in over 200 pellet implantations pellets were extruded from the site of the incision. Such complications may be avoided by placing the pellets a distance of at least 2.5 cm. from the margin of the incision. In no instance thus far has a local infection occurred at the site of the implantations.

2. *Specific:* Most of the complications which occur in patients with Addison's disease treated with desoxycorticosterone acetate (intramuscular injections of hormone in oil, pellets of crystalline hormone implanted subcutaneously or hormone administered sublingually) may be accounted for by one factor, i.e., *excessive retention of sodium chloride and water.* The extent to which untoward signs and symptoms develop is dependent upon

(*a*) the dose of hormone;
(*b*) the amount of sodium chloride in the diet and the supplementary sodium chloride therapy;
(*c*) predisposing factors in certain patients, such as heart disease, hypertension, hypoproteinemia, etc.

The nature of the complications which have arisen in 64 patients (Johns Hopkins Hospital) treated with synthetic hormone is summarized in table 14. *Hypertension* was noted at some time during therapy in 22 or 35 per cent of the patients. In most instances the hypertension was of a transient nature and occurred only during a period of excessive hormone and supplementary

TABLE XIV

Incidence of Complications Associated with Desoxycorticosterone Acetate Therapy (Johns Hopkins Hospital—64 Patients)

	Number of Patients	Per Cent
Hypertension*	22	34
Edema	17	27
Cardiac decompensation	5	8
Tendon "contractures"	2	3
Transient paralysis	1	2

* Systolic blood pressure exceeding 150 mm. Hg or diastolic blood pressure exceeding 100 mm. Hg or both, at some time during course of therapy.

sodium chloride therapy. In patients with Addison's disease in whom some degree of hypertension existed prior to the onset of adrenal cortical insufficiency there was a great predilection for the blood pressure to return to high levels and to remain there with only moderate doses of hormone.

Transient edema was noted in 14 (23 per cent) of the patients during desoxycorticosterone acetate therapy. In three of these patients the edema was rather extensive (anasarca). Edema was most frequently observed during the early weeks of therapy when an attempt was being made to determine the patient's optimum maintenance dose of hormone. The edema subsided rapidly following a reduction in the dose of hormone or upon withdrawing supplementary sodium chloride medication. In patients with long standing thrombophlebitis or lymphatic obstruction it was difficult to administer the optimum maintenance dose of hormone without at the same time inducing a moderate degree of localized edema in the affected part.

In five patients (8 per cent) continued synthetic hormone therapy accompanied by a marked increase in plasma volume, body weight, blood pressure and physical activity, ultimately induced signs and symptoms of circulatory failure. This complication occurred only in elderly patients or in patients in whom there had been some evidence of preëxisting myocardial damage or vascular disease. Circulatory failure may usually be avoided if care is exercised in restricting sodium chloride intake and in restricting activity during the early period of therapy during which blood volume, blood pressure and body weight are increasing rapidly. Treatment for this complication consists in absolute bed rest, digitalization, reduction in hormone and elimination of sodium chloride from diet. Subsequent rehabilitation should proceed slowly.

The long continued administration of even moderately excessive quantities of desoxycorticosterone acetate, or the synthetic hormone in conjunction with supplementary sodium chloride therapy may result in the excessive retention of sodium and chloride in the blood serum and tissues [14] associated with an abnormally low concentration of potassium. The resulting disturbance in sodium-potassium ratio, which is just the antithesis of the ratio which obtains in adrenal insufficiency (table 15) may give rise to unusual complications characterized by disturbances in neuromuscular function. In one patient (J. Z.) transient peripheral extensor motor paralysis was observed in conjunction with a low serum potassium concentration.[5] The

TABLE XV

Changes in Sodium to Potassium Ratio Which May Occur During Excessive Desoxycorticosterone Acetate Therapy

	Serum Sodium m.eq./l.	Serum Potassium m.eq./l.	$\frac{\text{Sodium}}{\text{Potassium}}$
Adrenal crisis	120	8.0	15
Adequate treatment	140	4.6	30
Excessive treatment	145	3.2	45

rapidity of onset, the absence of sensory disturbances and the rapid recovery without sequelae suggested an episode similar to that which is observed in familial periodic paralysis. Experimentally, similar disturbances have been noted in dogs treated with excessive doses of synthetic hormone in conjunction with supplementary sodium chloride.[15] As might be anticipated, a diet low in potassium content (of the type formerly recommended in the treatment of Addison's disease before the advent of desoxycorticosterone acetate) would facilitate these changes. For this reason it is urged that patients with Addison's disease treated with desoxycorticosterone acetate *not be given a diet of low potassium content!*

A second type of complication which has been observed in two of the 64 patients in our group, and in one patient in the outside group of 94 patients, consists of a painful and disabling contracture of the thigh muscles and tendons. The onset of this complication has occurred after several weeks or months of continued hormone therapy. Thus far it has been observed only in patients who have been incapacitated because of marked weakness or because of arthritic involvement of the knee joints. At the onset, because of the periarticular reference of the pain, it was thought that the patients were suffering from a relapse of the underlying arthritis. During the progress of the illness, the thighs slowly became flexed on the abdomen and the patients were unable to walk because of inability to straighten their legs. Roentgenograms of the joints revealed no evidence of progressive articular change. Although contractures conforming to this type have been seen in a patient with Addison's disease prior to therapy, it seemed probable that synthetic hormone therapy might have been a precipitating factor, since

in all three of these patients the onset of symptoms occurred after a continued period of hormone therapy. It is possible that this complication may be caused by excessive sodium and chloride retention in tissues, particularly tendons. No doubt inactivity and preëxisting joint disease predispose a patient to these changes.

Treatment of this complication, thus far, has been unsatisfactory. Obviously, sudden withdrawal of hormone would precipitate a crisis. Elimination of added sodium chloride therapy, reduction of synthetic hormone to a minimum maintenance dose, and supplementary potassium medication (potassium citrate solution 10 per cent; 30 to 45 c.c. in fruit juice daily) would be indicated if it could be proved that excessive sodium retention actually induced the change. In one patient we have resorted to orthopedic measures (traction followed by manipulation under anesthesia), since a trial on the above regimen, and a continued period of adrenal cortex extract therapy did not result in any appreciable improvement in this patient. Attention is called to this condition particularly because of the ease with which it may be confused with the muscular pains (low-sodium cramps) which are commonly observed in patients in adrenal insufficiency. For the latter, sodium chloride and hormone are specific.

Although desoxycorticosterone is closely related chemically to progesterone we have not, to date, observed any evidence of progestational changes in female patients with Addison's disease who have been treated for long periods of time with the synthetic adrenal cortical hormone. Several patients have noted increased turgor of the breasts. It seems reasonable to assume that this change may be accounted for by an increased accumulation of extracellular fluid which occurs during adrenal cortex hormone therapy.

Cardiac Changes in Addison's Disease: It has long been known that the heart in patients with Addison's disease is smaller than normal [7] and that the electrocardiogram in many of these patients shows abnormalities suggesting disease of the myocardium.[16, 17] Recent studies [4, 18, 19, 20] have demonstrated that progressive cardiac enlargement may occur in patients with Addison's disease following overdosage with desoxycorticosterone acetate. It seems probable that preëxisting cardiac disease may play an important rôle in predisposing certain patients to myocardial failure following excessive desoxycorticosterone acetate therapy. The poor physical condition of untreated patients with Addison's disease makes a study of cardiac reserve difficult, if not impossible, prior to therapy. Investigation of the effect of synthetic hormone therapy on cardiac function, therefore, is dependent chiefly on a study of the progressive changes in electrocardiograms and teleroentgenograms.

The effect of synthetic hormone therapy on changes in cardiac diameter was followed closely in 46 of our 64 patients studied (table 16). In no patient did the heart-to-chest ratio exceed 50 per cent prior to therapy. In two patients during therapy the ratio exceeded 50 per cent and both of these

TABLE XVI

Effect of Desoxycorticosterone Acetate Therapy on Cardiac Diameter (46 patients)

	Heart to Chest Ratio	Range
Prior to treatment	38.6%	(28–46)
Maximum measurement during treatment	42.2%	(32–55)
Present status (approx. 2 yrs. therapy)	41.3%	(32–50)

patients were among the five who developed signs of circulatory insufficiency. With care in the regulation of the dose of hormone and supplementary sodium chloride medication, only a moderate increase in heart size occurred during a period of approximately two years of treatment, viz., 38.6 per cent heart-to-chest ratio prior to therapy; present status 41.3 per cent heart-to-chest ratio.

Electrocardiograms were analyzed in 58 of our 64 patients to determine the incidence of abnormal changes without regard to therapy (tables 17 and 18). There were significant electrocardiographic changes in 35 of the patients (60 per cent). In 17 patients (29 per cent) the changes suggested definite myocardial damage. A high incidence of abnormal electrocardiograms appeared in all age groups (table 17). It is interesting to note that 19 of the patients (54 per cent) with abnormal electrocardiograms were under 40 years of age.

The group of 35 patients with abnormal electrocardiograms included one patient with clinical evidence of arteriosclerotic heart disease and two patients with clinical evidence of rheumatic heart disease. There was clinical evidence of arteriosclerosis in seven patients and of rheumatic heart disease in three patients in the entire group of 64 patients.

TABLE XVII

Electrocardiographic Findings in Addison's Disease (58 patients)

Age Group (years)	Number of Patients	Electrocardiographic Interpretation			
		Normal	"Borderline" *	Myocardial Damage †	Per Cent Abnormal
20–29	16	7	5	4	56
30–39	18	8	4	6	56
40–49	13	6	4	3	54
50–59	8	1	3	4	88
60–69	3	1	2	0	67
TOTAL	58	23	18	17	60

* The term "borderline" has been used to indicate the presence of abnormal electrocardiographic changes which are believed to be significant, although not indisputable evidence of myocardial damage. These changes were as follows: PR interval over .21 second; prolonged QT interval (by formula of Ashman and Hull [21]); QRS voltage less than 5 mm. in Leads I, II, III and/or Lead IV F; isoelectric T_1 or T_2; negative T_4; initial upward QRS deflection in Lead IV F absent or less than 1 mm.; ST segment deviation of less than 1 mm.

† As indicated by inverted T_1 and/or T_2, isoelectric T-waves in all leads, or the presence of combinations of three or more of the "borderline" changes.

TABLE XVIII
Incidence of Electrocardiographic Changes in Addison's Disease (58 patients)

Change	Number of Patients	Per Cent
Prolonged PR interval*	12	21
Prolonged QT interval*	15	26
Low voltage (QRS)*		
Leads I, II, III	11	19
Lead IV F	9	16
Low or isoelectric		
T_1	19	33
T_2	19	33
T_4	4	7
Diphasic or Negative		
Ti	5	9
T_2	11	19
T_3	39	67
T_4	19	33

* See footnote to table 17.

The preponderance of females among the patients with abnormal electrocardiograms is of interest. Twenty (57 per cent) of the 35 patients with significant electrocardiographic changes were females (chart 5). Of the 26 females studied 77 per cent had abnormal electrocardiograms, whereas only 47 per cent of the males were in this group. The explanation for this

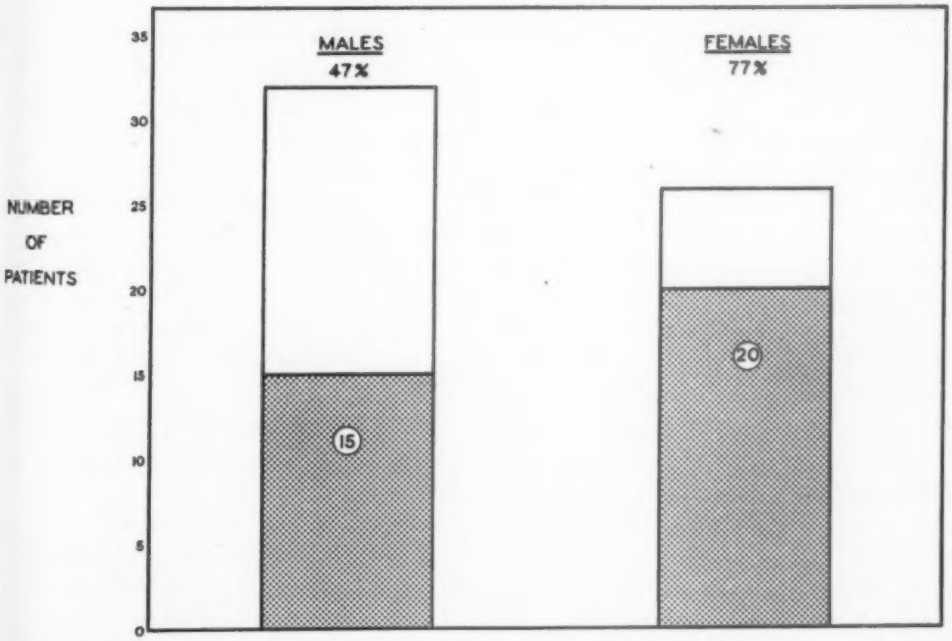

CHART 5. Electrocardiographic abnormalities in Addison's disease (sex incidence) ▩ patients with abnormal electrocardiograms.

Males: "borderline" changes—9; myocardial damage—6. Females: "borderline" changes —9; myocardial damage—11.

greater frequency of abnormal electrocardiographic changes in the females is not apparent. However, in support of this apparently higher incidence of cardiac abnormalities in female patients is the fact that five of the seven deaths which could be attributed to cardiovascular disease (entire group of 158 patients, table 12) occurred in female patients.

There appeared to be no pattern of electrocardiographic changes specific for Addison's disease. A wide variation characterized the changes, viz., prolonged PR and QT intervals, low QRS voltage, and low or inverted T-waves. The incidence of these findings in this group of patients was considerably higher than that reported recently for a normal population.[22, 23] Other significant electrocardiographic changes observed less frequently were: an absence of the initial upward QRS deflection in the chest lead (two patients), small initial upward QRS deflection in the chest lead (seven patients), sinus bradycardia with cardiac rate of less than 50 per minute (five patients), premature ventricular contractions (four patients) and ST segment depression of less than 1 mm. (four patients).

In no instance was an electrocardiogram included in this series which had been taken during digitalis therapy or within three weeks after digitalis therapy had been discontinued. Since no attempt was made to standardize the position of patients during the recording of electrocardiograms, it is possible that in some instances inversion of T_2 actually represented a change related to the sitting position.[24] In no patient in this series, however, did the interpretation of myocardial damage depend solely upon the presence of inversion of T_2.

Effect of Desoxycorticosterone Therapy upon the Electrocardiogram in Addison's Disease: The relation of potassium retention to changes in the electrocardiogram has been reported in experimental adrenal insufficiency.[25] The abnormal electrolyte pattern is restored to normal in adrenalectomized animals and in patients with Addison's disease by desoxycorticosterone acetate therapy. Excessive desoxycorticosterone acetate therapy can produce an abnormal electrolyte pattern in both the blood serum and tissues, i.e., high sodium, low potassium.[14] Presumably changes in the electrocardiogram could accompany these disturbances in electrolyte concentration. Changes in the electrocardiogram associated with low serum potassium have been observed in a patient with familial periodic paralysis.[26] The relation of the disturbances in electrolyte metabolism to changes in carbohydrate metabolism and cardiac function is not fully understood.

Electrocardiograms were recorded in 28 patients before desoxycorticosterone therapy was begun and repeated during therapy (1.4 years, average duration of therapy—tables 19 and 20). In 13 additional patients electrocardiograms were taken after desoxycorticosterone therapy had been begun. Of this total group of 41 patients, seven showed significant improvement in the electrocardiogram during therapy, whereas 14 showed an increase in the number and extent of the abnormalities. Five of the seven instances of

improvement were related to recovery from periods of inadequate therapy or of overdosage with hormone. In contrast, only two of the 14 instances of impairment of the electrocardiogram coincided with a period of unfavorable clinical response. The remaining 12 patients showed a moderate to marked improvement in well-being, at the time that the electrocardiogram

TABLE XIX

Changes in Electrocardiograms Which Occurred During Desoxycorticosterone Acetate Therapy (Addison's Disease)

	Number of Patients	Electrocardiographic Interpretation			
		Normal	"Borderline" *	Myocardial Damage	Per Cent Abnormal
Prior to hormone therapy	28	19	6	3	32
Following 1.4 years of continuous hormone therapy	28	12	8	8	57

* See footnote to table 17.

TABLE XX

Incidence of Electrocardiographic Changes in 28 Patients with Addison's Disease Prior to and During Desoxycorticosterone Acetate Therapy

	* Prolonged PR Interval	* Prolonged QT Interval	* Low QRS Voltage		Low or Isoelectric			Diphasic or Negative			
			I II III	IV	T_1	T_2	T_4	T_1	T_2	T_3	T_4
Prior to desoxycorticosterone acetate therapy	0	2	4	2	4	2	3	0	4	11	4
During desoxycorticosterone acetate therapy (1.4 yrs.)	9	10	5	2	6	5	2	5	11	19	8

* See footnote to table 17.

was giving evidence of progressive myocardial involvement. The most striking abnormalities developing under desoxycorticosterone therapy were prolongation of the PR interval (10 patients) and prolongation of the QT interval (10 patients). No patients showed a prolonged PR interval before receiving synthetic hormone (table 20). T-wave inversion suggesting diffuse myocardial damage or coronary insufficiency appeared in six patients, three of whom had had normal and three of whom had had "borderline" electrocardiograms before treatment.

The number of patients showing myocardial damage increased from three to eight during desoxycorticosterone therapy in the group of 28 patients in whom records were available prior to treatment with synthetic hormone (table 19). No increase in the number of patients with electrocardiographic abnormalities occurred in the smaller group of 13 patients in whom records were made only during the period of desoxycorticosterone

TABLE XXI

Summary of Electrocardiographic Findings in Patients with Addison's Disease prior to and during Desoxycorticosterone Acetate Therapy

	Number of Patients	Duration of Hormone Therapy (years)	Electrocardiographic Interpretation							
			Normal		* Borderline		Myocardial Damage		Abnormalities	
			1st ECG	Present	1st ECG	Present	1st ECG	Present	1st ECG	Present
Serial electrocardiograms prior to and during hormone therapy	28	1.4	19	12	6	8	3	8	32%	57%
Serial electrocardiograms during hormone therapy (no record prior to therapy)	13	2.1	4	4	7	8	2	1	69%	69%
Single electrocardiograms prior to hormone therapy (none since)	9	0	6	—	3	—	0	—	38%	—
Single electrocardiograms during hormone therapy	8	0.8	—	5	—	1	—	2	—	38%
Total: electrocardiograms prior to hormone therapy	37	—	25	—	9	—	3	—	32%	—
Total: electrocardiograms during hormone therapy	49	1.5	—	21	—	17	—	11	—	57%

*See footnote to table 17.

therapy (table 21). This difference in the two groups did not appear to be related to the duration of Addison's disease or to the clinical response to therapy, but may indicate that electrocardiographic abnormalities make their appearance early during the period of rapid clinical improvement which follows the *initiation* of desoxycorticosterone therapy. It is possible that in untreated patients myocardial disease may be masked by the decreased demands made on the heart by the lowered arterial pressure and reduced blood volume of patients in adrenal insufficiency. By elevating blood pressure and restoring blood volume, desoxycorticosterone therapy disturbs this balance, increases the cardiac load, and may thereby lead to electrocardiographic abnormalities in patients with latent myocardial damage.

Electroencephalographic Changes in Addison's Disease: Electroencephalograms * were recorded in 36 of the 64 patients under our observation. Definite abnormalities were noted in 25 or 69 per cent of these 36 patients. The abnormal features in most instances consisted of one or more of the following changes:

(1) regular occurrence of oscillations slower than the normal alpha rhythm with a predilection for the frontal areas, not influenced by opening the eyes.

(2) absence of, or greatly decreased number of low voltage, fast frequency waves (beta waves).

(3) increased sensitivity to hyperventilation.

Unfortunately in the majority of patients it was not possible to obtain electroencephalographic records prior to synthetic hormone therapy. However, in two of the three patients who were studied before therapy had been instituted, changes similar to those noted above were observed. The effect of desoxycorticosterone therapy on the electroencephalographic records was unpredictable. Four patients with normal electroencephalograms, early in the course of therapy, also had normal tracings after 4 to 27 months of continued hormone therapy. Four patients with abnormalities in the electroencephalograms early in the course of synthetic hormone therapy showed no progression of the abnormal changes during the subsequent 12 months of treatment. Three patients, however, showed a pronounced increase in the abnormal electroencephalographic features during a 12 month period of desoxycorticosterone acetate treatment. In contrast to these evidences of progressive change in the resting pattern of the electroencephalogram during hormone therapy, four patients were observed to have a pronounced decrease in the abnormal sensitivity to hyperventilation during a 12 month period of synthetic hormone therapy.

The situation in relation to the changes in the electroencephalogram of patients with Addison's disease treated with desoxycorticosterone acetate is

* We are greatly indebted to Dr. W. Christie Hoffmann of the Henry Phipps Psychiatric Clinic for the encephalographic records. A complete study of the electroencephalographic changes in these patients has been prepared for publication.[27]

somewhat analogous to that which was observed in relation to the abnormal electrocardiographic changes in the same group of patients. In both instances typical abnormalities were present before synthetic hormone therapy was instituted, and in most instances continued synthetic hormone therapy failed to correct the abnormalities despite striking evidence of clinical improvement. Although in both instances it was thought likely that the extensive and progressive changes in electrocardiogram and electroencephalogram might be correlated with the degree to which carbohydrate metabolism was impaired in these patients, such a correlation was not present in all cases. A higher incidence of abnormal electroencephalograms was noted in male patients in contrast to the predominance of abnormal electrocardiograms which was observed in female patients.

Metabolic Studies

A. Plasma Electrolytes and Plasma Volume: A striking increase in plasma volume is one of the first changes which is noted in patients with Addison's disease under desoxycorticosterone acetate treatment.[2] If not measured directly, some idea of the magnitude of the increase in plasma volume can be obtained from the changes in hematocrit, red blood cell count and serum protein concentration which occur during the first few days of therapy. In addition to the prompt increase in plasma volume there is also a restoration of the plasma concentration of sodium, chloride, potassium and non-protein nitrogen to normal levels. During treatment with synthetic hormone the renal excretion of sodium and chloride is decreased (positive balance), whereas the excretion of potassium and inorganic phosphorus is increased (negative balance). Withdrawal of hormone therapy is followed rapidly by increased excretion of sodium, chloride and water, weight loss, decrease in plasma volume, decrease in *total plasma content* of sodium and chloride, retention of potassium and inorganic phosphorus associated with an increase in the concentration of potassium in plasma.[2] Patients may improve remarkably during the early period of therapy without necessarily showing any increase in plasma concentration of sodium and chloride; ultimately, however, these values attain normal levels. Conversely, sudden withdrawal of hormone therapy may temporarily precipitate a crisis without necessarily effecting a significant reduction in the concentration of sodium and chloride in the plasma. This apparent lack of correlation between changes in clinical state and changes in plasma concentration of electrolytes can be understood if plasma volume measurements are made during these periods, since it can be readily demonstrated that during the early period of treatment there is an appreciable *increase in the total plasma content of sodium and chloride* and that immediately following withdrawal of therapy there is a *reduction in the total plasma content of these ions.* Whether or not corresponding changes take place in the plasma concentration of these ions depends upon the relative gain or loss of water.

The changes which occurred in blood sugar and non-protein nitrogen levels, as well as plasma sodium, potassium, chloride and carbon dioxide combining power, hematocrit and serum protein concentration during desoxycorticosterone acetate in 44 of our 64 patients are summarized in table 22. It is of particular interest to note that the fasting blood sugar level

TABLE XXII

Blood Chemical Changes in Patients with Addison's Disease During Desoxycorticosterone Acetate Therapy

Number of Patients	Blood Chemical Constituent	Mean Value Prior to Therapy	Mean Value during Therapy	Difference Between Means * / Standard Deviation of the Distribution of the Means
40	Serum sodium m.eq./l.	132.3	141.3	4.5
41	Serum chloride m.eq./l.	97.5	104.3	4.2
38	Carbon-dioxide combining capacity	24.2	26.0	2.9
44	Serum potassium m.eq./l.	5.7	4.4	5.0
42	Non-protein nitrogen mg./100 c.c.	34	28	3.6
42	Blood sugar mg./100 c.c.	87	81	2.7
42	Hematocrit (per cent cell volume)	41.4	36.5	4.5
37	Serum protein gm./100 c.c.	6.3	5.7	3.7

* The difference between means is significant when the value of this factor is greater than 2.

$$\sqrt{\frac{\sigma_g^2}{N}}$$

Standard deviation of the distribution of means of individual changes.

N = Number in series

$\sigma_g = \sqrt{\frac{(X_1 - X_2)^2}{N}}$ = Standard deviation of the distribution of individual changes

$(X_1 - X_2)^2$ = Sum of squares of difference in means in series 1 and 2 (the two series being compared)

N = number in series

$\bar{X}_1$ = Mean of series 1

$\bar{X}_2$ = Means of series 2

If $\frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{\sigma_g^2}{N}}} > 2$, difference of $\bar{X}_1 - \bar{X}_2$ is significant.

(Note that N occurs in this formula twice—once as a part of γ_g^2.)

prior to desoxycorticosterone acetate therapy was significantly higher than during therapy. This suggests that not only does desoxycorticosterone acetate lack the carbohydrate-stimulating quality of certain adrenal cortical steroids, but that it may actually exert a slight insulin-like action. The changes in serum electrolyte concentration which occurred during synthetic hormone therapy were significant and were consistent with the changes reported previously.[2]

B. Basal Metabolic Rate: In an earlier report [11] it was shown that a basal metabolic rate of less than — 20 per cent of standard was unusual in

patients with Addison's disease uncomplicated by thyroid or pituitary deficiency. Furthermore, it was shown that in a group of seven patients no significant change in basal metabolic rate was noted following continued treatment with desoxycorticosterone acetate, the average value before treatment being — 10 per cent (18 determinations) and during treatment — 12 per cent (10 determinations). The basal metabolic rates of 55 of the 64 patients in the Johns Hopkins Hospital group have been measured on several

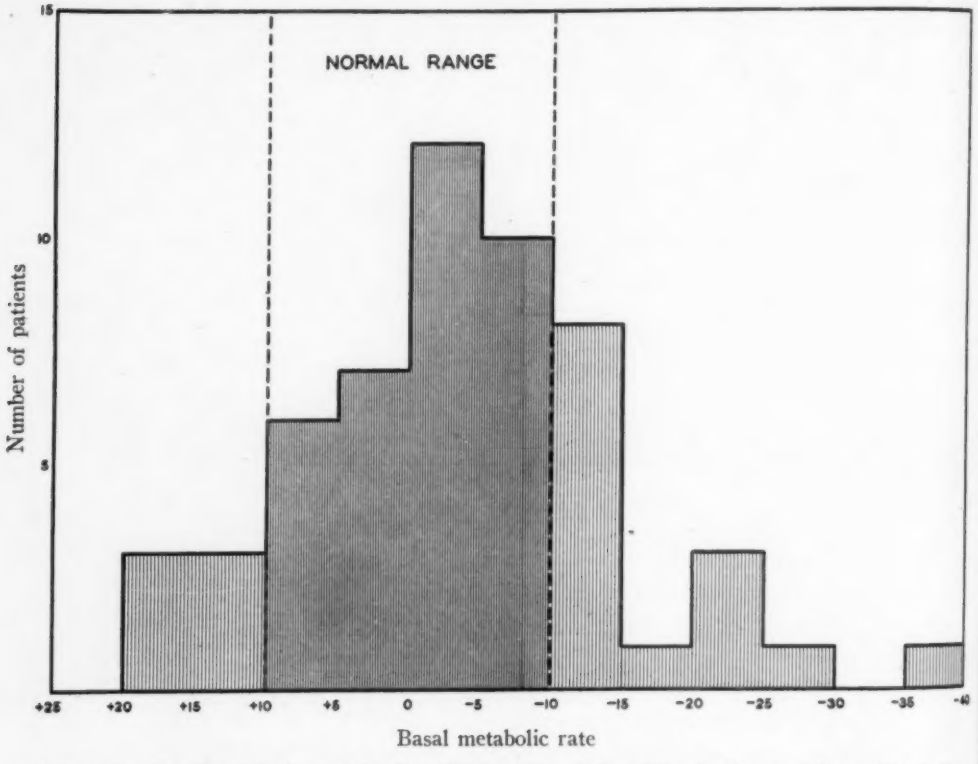

CHART 6. Basal metabolic rate in fifty-five patients with Addison's disease (Johns Hopkins Hospital) during treatment with desoxycorticosterone acetate.

occasions during desoxycorticosterone acetate therapy. The average value of these determinations for each patient is presented in chart 6. It is to be noted that the values for 35 patients or 64 per cent of the group lie between + 10 per cent and — 10 per cent of standard. In six patients the values exceeded + 10 per cent and in 14 patients the values were below — 10 per cent, five of the latter being below — 20 per cent. All five of this latter group presented definite clinical evidence of thyroid deficiency.

C. Pigmentation: Abnormal pigmentation was present in 60 (94 per cent) of the 64 patients in our group. Vitiligo was present in eight, or 13 per cent, of these 60 patients. The occurrence of vitiligo in the presence of

adrenal cortical deficiency was pointed out by Addison in his original monograph.[7]

In considering the type of abnormal pigmentation which may occur in patients with Addison's disease it may be helpful to list the variety of changes which have been observed in the present group of patients, viz.:

1. Bluish-black discolorations which appear on the lips, gums and on the mucous membranes of the mouth, rectum and vagina. It should be pointed out that this type of pigmentation occurs normally in negroes and in certain southern European races.
2. A diffuse tan over the non-exposed as well as the exposed portions of the body.
3. Hyperpigmentation of the extensor surfaces of the body, pressure points, scars and lines on the palms of the hands.
4. Multiple black freckles, distributed most commonly over the forehead, face, neck, shoulders and arms.
5. Areas of vitiligo or leukoderma. The appearance of these areas is usually striking because of the hyperpigmentation of the surrounding skin.

It is not possible to predict what change, if any, may occur in the pigmentation of patients with Addison's disease during treatment with desoxycorticosterone acetate. In all patients there is a noticeable lightening of the complexion within a few days after hormone therapy is instituted. This immediate change reflects the hemodilution and increase in peripheral circulation which has occurred as a result of sodium, chloride and water retention, increase in plasma volume and increase in blood pressure. During periods of insufficient therapy patients rapidly assume a much darker complexion.

In the majority of patients during long continued hormone therapy there has been some decrease in the intensity of the abnormal pigmentation (table 23) and in a few patients there has been complete disappearance of small localized areas of increased pigmentation. In two patients, despite continued hormone therapy, there has been a slow but progressive increase in pigmentation.

It is well known that the margins of scars which occur in patients with Addison's disease are a frequent site for increased pigment deposition. For this reason the small scars which are made in the infrascapular region during the implantation of pellets may provide an excellent indicator of the change in pigment metabolism which occurs during therapy. A striking pigmentation of the margins of these scars following the implantation of pellets of desoxycorticosterone acetate strongly suggests that the abnormality in pigment metabolism has not been corrected by synthetic hormone therapy, whereas failure of the margins of these scars to become pigmented suggests that the progress of the abnormal process has been arrested.

D. Creatine Metabolism: The presence of spontaneous creatinuria associated with a decrease in creatine tolerance has been observed in untreated

patients with Addison's disease.[7, 28] Treatment with whole adrenal cortex extract was followed by improved appetite, increased ingestion of food, gain in weight and improved clinical condition. Under these circumstances spontaneous creatinuria disappeared and creatine tolerance improved.[29] It was not known whether the beneficial effect of adrenal cortex extract represented a specific effect of certain adrenal steroids on phosphocreatine metabolism or whether the improvement was merely a reflection of the improved nutritional state induced by hormone therapy.

TABLE XXIII

Changes in Pigmentation Which Occurred in 64 Patients (Johns Hopkins Hospital) with Addison's Disease during Desoxycorticosterone Acetate Therapy

	Number of Patients	Per Cent of Total of 64 Patients
Abnormal pigmentation	60	94
Vitiligo	8	13
No significant change in pigmentation during therapy	33	52
Definite decrease in pigmentation	25*	40
Complete restoration to normal	0	0
Increase in pigmentation	1	2
First appearance of pigmentation *during* therapy	1	2

* Six patients in this group exhibited a striking decrease in pigmentation as a result of a marked increase in the extension of the areas of vitiligo.

With the exception of one patient (A. H., chart 7), it was not possible to study the disturbance in creatine metabolism prior to the institution of desoxycorticosterone acetate therapy. The status of creatine metabolism in 15 patients, however, was investigated at a later date (following one year of continuous synthetic hormone therapy). In seven of the 16 patients (44 per cent) spontaneous creatinuria of more than 100 mg. per day was observed at this time. (The patients were maintained on a creatine-low diet during these tests.) The nutritional state and appetite of the patients at the time of these observations were good. Retention of administered creatine (chart 7) was definitely impaired in 10 of the 16 patients or 63 per cent during synthetic hormone therapy, as well as in patient A. H., prior to the institution of therapy (chart 7).

It is evident from these data that creatine metabolism was abnormal during synthetic hormone therapy in a high proportion of the patients who were tested. There was no indication that prolonged treatment resulted in progressive improvement in creatine metabolism. In two patients who received long continued therapy with adrenal cortex extract (5 to 10 c.c. daily) a high normal retention of administered creatine (97.0 and 94.9 per cent respectively) was noted.

It appears probable that the abnormality in creatine metabolism which occurs in patients with Addison's disease is aggravated by anorexia and

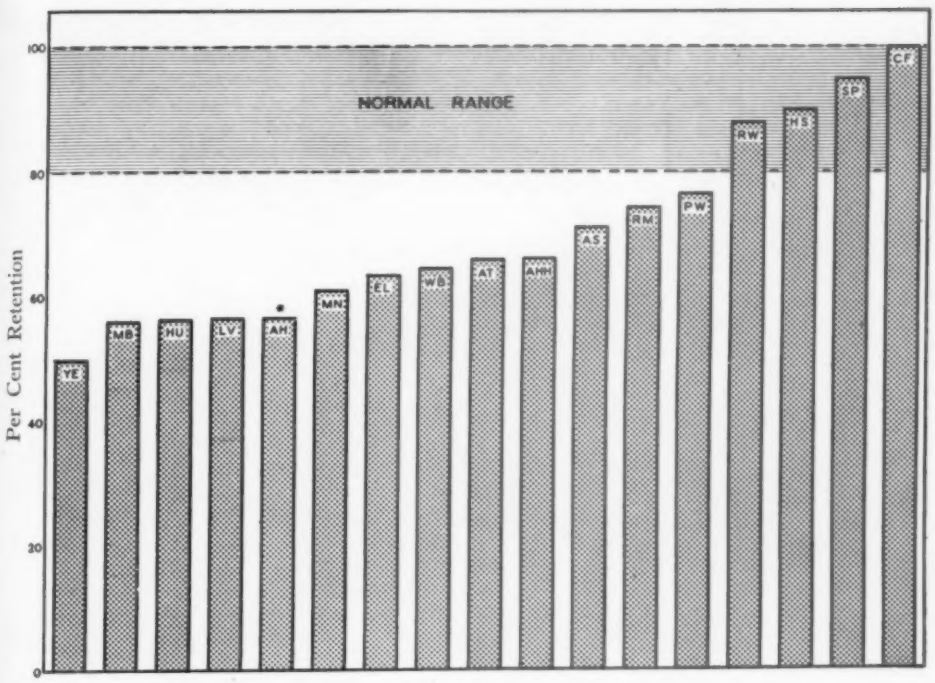

CHART 7. Creatine tolerance test * in patients with Addison's disease treated with desoxycorticosterone acetate. Creatine retention following test dose 2.64 gm.

inanition but is certainly not dependent upon these factors. Desoxycorticosterone acetate therapy does not correct the abnormality in creatine metabolism, whereas earlier studies [28, 29] and the studies on two patients in the present series suggest that treatment with adequate quantities of whole adrenal cortex extract may correct the underlying disturbance in creatine metabolism.

E. Renal Function: Renal function may be temporarily reduced during adrenal crisis as a consequence of reduced blood volume and reduced blood pressure. At this time there may occur a rise in blood non-protein nitrogen. Treatment with adrenal cortex extract or synthetic desoxycorticosterone acetate is followed by a rapid improvement in renal function.

One practical difficulty which arises in carrying out renal function tests in patients with Addison's disease is the inability in many instances to obtain a satisfactory rate of urine formation. This may result from the fact that these patients frequently experience considerable difficulty in ingesting large quantities of water, and furthermore, the absorption of water from the intestinal tract may occur at a rate slower than normal.

* Patients were maintained on a diet of low creatine content for a period of at least 72 hours prior to these determinations. On the day of the creatine tolerance test 2.64 gm. of creatine were administered by mouth. Details of the test and the technical methods employed have been described elsewhere.[30]

Patient A. H. was tested prior to the institution of therapy.

A summary of the results of the phenolsulphonphthalein and urea clearance tests in 55 of the 64 patients in our group is presented in table 24. Inulin and diodrast clearances were not measured in these patients. Talbott, recently, has made a number of very careful observations on the status of renal function in patients with Addison's disease.[31] He has demonstrated that although the phenolsulphonphthalein excretion and urea clearance may appear to be normal, more exact methods frequently demonstrate an appreciable degree of renal insufficiency.

TABLE XXIV

Summary of Renal Function Tests in 55 Patients with Addison's Disease Treated with Desoxycorticosterone Acetate (Johns Hopkins Hospital)

	Number of Patients	Per Cent of Total of 55 Patients
Phenolsulphonphthalein Test		
Less than 40% excretion in 1 hour	5	9
Less than 60% excretion in 2 hours	9	16
Urea Clearance		
Less than 60% standard clearance	3	5

F. Hepatic Function: It is well known that the tolerance of adrenalectomized animals and patients with Addison's disease to various toxic agents is greatly reduced. One theory regarding the action of adrenal cortical hormone postulates that an important function of this hormone is its ability to assist the body in processes involving the detoxification of noxious substances.[32]

Rowntree and Snell [7] investigated hepatic function in patients with Addison's disease by studying the bilirubin content of the serum and retention of bromsulphthalein. The serum bilirubin level was uniformly normal, but the results of the bromsulphthalein test suggested slight impairment of liver function. We have studied the excretion of hippuric acid after intravenous injection of a standard dose of sodium benzoate in nine patients with Addison's disease during treatment with desoxycorticosterone acetate. In all instances the values obtained were distinctly below those observed in normale subjects (chart 8). It is of interest that four of the nine patients showed moderate splenomegaly. In no instance was there evidence of impaired renal function. It is possible that the impaired conversion of sodium benzoate to hippuric acid may reflect a defect in hepatic function occasioned by prolonged glycogen depletion or may be the result of impaired amino acid metabolism (glycine).

Intercurrent Infections: In the group of 64 patients treated in the Johns Hopkins Hospital, intercurrent infections played a significant rôle (a) as a precipitating factor in the original episode of adrenal insufficiency, (b) as a complication in the course of subsequent hormone therapy, and (c) as one of the chief causes of death. Ten patients definitely dated the onset of Addi-

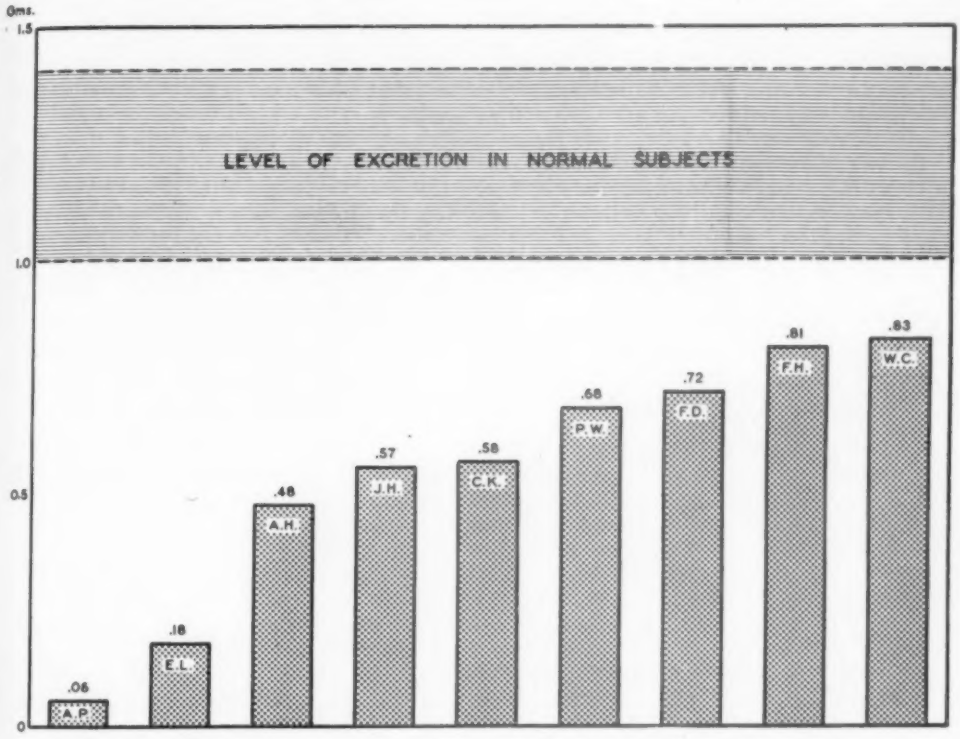

CHART 8. Hippuric acid excretion in patients with Addison's disease treated with desoxycorticosterone acetate. Excretion of hippuric acid patients.

son's disease to an acute febrile episode which was diagnosed in eight cases as "influenza," in one case as scarlet fever, and in one case as infectious mononucleosis. Exacerbation of adrenal insufficiency following acute infections occurred in 16 of the patients during treatment with synthetic hormone. In several of these patients repeated exacerbations of the disease occurred with successive bouts of infection. In five of the patients (8 per cent) crises induced by acute infections led to death. Infections due to hemolytic streptococci were one of the most common types encountered.

A striking characteristic of the response of patients with Addison's disease to acute infections was the extreme rapidity with which they became prostrate. On several occasions severe adrenal crisis with shock occurred within 48 hours of the onset of the acute infection. The increase in hormone requirement was very great during this period. Thus the problem of immediate and intensive early treatment had to be met. It is to be noted that although patients treated with synthetic hormone may experience a crisis induced by an acute intercurrent infection, the convalescence of these patients is very rapid in comparison with the prolonged period of invalidism previously observed in patients with Addison's disease.

Extremely encouraging results have been obtained recently in two patients with acute hemolytic streptococcus infection in which *sulfadiazine* was used in conjunction with adrenal cortex extract, desoxycorticosterone acetate and intravenous infusion of sodium chloride and glucose solution.[13] Sulfadiazine appears to be the most desirable of the sulfonamide drugs in treating patients with Addison's disease because of the low incidence of nausea and vomiting associated with its administration. The basic routine treatment which was employed in these two patients is similar in every respect to that outlined in "the treatment of adrenal crisis," the only difference being the addition of sulfadiazine therapy. An initial dose of 4 to 5 gm. of the sodium salt was given intravenously in conjunction with the infusion of saline and glucose solutions as soon as the patient was seen. Subsequently 1 gm. of sulfadiazine was given by mouth every four to six hours and an attempt was made to maintain a blood level of 10 to 20 mg. per 100 c.c. as long as fever persisted. In the event that sulfadiazine could not be taken by mouth, the intravenous injection of sodium salt of sulfadiazine (2 gm.) was repeated at 8 to 12 hour intervals. The importance of administering large quantities of adrenal cortex extract at frequent intervals, in conjunction with saline and glucose infusions and a supplementary dose of desoxycorticosterone acetate has been pointed out. The prompt recognition of infections and the appreciation of the necessity for immediate hospitalization with intensive therapy should do much toward reducing the relatively high mortality rate from hemolytic streptococcus infections in patients with Addison's disease. It is apparent that the hormone requirement of patients who have recently experienced an acute infection may be temporarily and even permanently increased.

Effect of Pregnancy: In one patient (H. B.) signs of adrenal insufficiency became manifest during pregnancy. In two other patients (K.D., and M.P.) an increase in pigmentation which was not considered to be beyond normal was noted during pregnancy. However, following the termination of pregnancy, the pigmentation in these two patients became progressively more intense instead of diminishing. In two patients (R. G., and M. P.) the first episode of adrenal crisis was precipitated by delivery. In one patient (A. K.) interruption of pregnancy was followed by septicemia and death. At present one patient (K. D.) is again pregnant.

The early weeks of pregnancy are especially difficult for patients with Addison's disease because of the associated nausea and vomiting. During this period it may be necessary to supplement desoxycorticosterone acetate treatment with daily injections of adrenal cortex extract and infusions of saline and glucose. The latter months of pregnancy should be rather well tolerated because of the sodium-retaining effect of the sex hormones,[33] and the secretion of the fetal adrenal. It has been demonstrated repeatedly that the hormone requirement of adrenalectomized animals is greatly reduced during pregnancy,[34, 35] and the beneficial effect of progesterone on the life

maintenance of adrenalectomized animals is well known.[36] Desoxycorticosterone acetate treatment during the latter months of pregnancy should be regulated carefully to prevent excessive sodium and chloride retention.

The period immediately following delivery may prove to be a very critical one for patients with Addison's disease. Blood loss, the removal of supplementary adrenal cortical hormone provided by the fetus and the rapid decrease in titer of sex hormones may readily induce a crisis. Collapse at the time of delivery may result in hemorrhage into the anterior pituitary with resulting pituitary deficiency.[37] Therefore, patients with Addison's disease should be treated for impending crisis immediately prior to delivery (see section on preoperative therapy).

Although pregnancy is distinctly contraindicated in patients with Addison's disease, once established, it is probably much safer to attempt to carry the pregnancy to termination unless very unusual complications supervene. The need for hospitalization and careful supervision at the time of delivery should be emphasized.

Surgery in Addison's Disease: Patients with Addison's disease have long been known to represent extremely poor surgical risks.[7] Minor operative procedures such as dental extractions have been known to precipitate a crisis, and major operative procedures frequently resulted in death. Several factors contribute to the poor response of patients with Addison's disease to surgical procedures:

1. Lowered tolerance to narcotics and anesthetics.
2. Hypotension.
3. Dehydration and reduced plasma volume.
4. Depleted carbohydrate reserves.
5. Myocardial damage.

The first four of these disturbing factors may be corrected by adequate treatment with adrenal cortex extract, desoxycorticosterone acetate and intravenous infusions of saline and glucose solutions. At present with the improved management of patients it is possible to carry patients successfully through major operative procedures. A comparison has been made between the effect of surgery on patients prior to therapy (and in some instances prior to the diagnosis of Addison's disease) and subsequently (table 25). All seven patients did very poorly following operative procedures which were carried on prior to specific therapy. In five of these seven patients it appeared that the operative procedure hastened the development of the classical clinical picture of the disease (table 25, Section *A*). Of the seven treated patients (table 25, Section *B*), six had an uneventful postoperative course with the exception, in one patient, of a rather mild hypoglycemic episode during the second postoperative day. The seventh patient died on the forty-first postoperative day following a therapeutic abortion complicated by perforation of the uterus, pelvic vein thrombophlebitis, mul-

TABLE XXV

Complications of Surgical Operations in Patients with Addison's Disease

A.

Patient	Sex	Present Age	Operation	Hormone Therapy	Remarks
F. H.	M	24	Appendectomy	0	Precipitated adrenal crisis.
R. G.	F	28	Hysterectomy	0	Crisis, onset of Addison's disease.
R. M.	F	36	Tonsillectomy	0	Crisis, onset of Addison's disease.
E. V.	M	43	Cholecystectomy	0	Stormy postoperative period, onset of Addison's disease.
A. H.	F	40	Dental extraction	0	Crisis.
H. S.	M	49	Tonsillectomy	0	Stormy postoperative period, onset of Addison's disease.
A. S.	F	46	Hysterectomy	0	Prolonged convalescence, onset of Addison's disease.

B.

D. B.	M	36	Herniorrhaphy	Desoxycorticosterone acetate	Uneventful convalescence.
E. F.	F	50	Dental extraction	Desoxycorticosterone acetate	No complications.
F. H.	M	24	Tonsillectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.
A. H.	F	41	Hemorrhoidectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.
A. K.	F	32	Therapeutic abortion	Desoxycorticosterone acetate	Septicemia, death.
F. G.	F	32	Appendectomy	Desoxycorticosterone acetate.	Uneventful convalescence.
J. P.	M	22	Nephrectomy	Desoxycorticosterone acetate+adrenal cortical extract.	Immediate postoperative course excellent, late convalescence complicated by excessive sodium retention, present health excellent.
A. S.	M	35	Epididymectomy	Desoxycorticosterone acetate+adrenal cortex extract.	Uneventful convalescence.

tiple pulmonary infarcts, severe pyelitis and *B. coli* bacteremia. It is of interest to note that this patient's blood pressure was maintained at a level of 125 mm. Hg systolic and 80 mm. diastolic until shortly before death.

Technic for Preparing Patients with Addison's Disease for Surgery: Local anesthesia is used whenever possible. When necessary a general anesthetic may be used, but care should be taken not to use anesthetic agents which *induce an appreciable degree of anoxia.* The ideal general anesthetic for patients with Addison's disease is yet to be discovered. It is possible that cyprethylene may prove to be the best for these patients. Cyclopropane

has been used successfully, although the undesirable features of using this anesthetic in general operating rooms is well known. Pre-anesthetic morphine is given in reduced dosage, i.e., 5 to 10 mg. instead of 10 to 15 mg. It is our custom to give adrenal cortex extract and desoxycorticosterone acetate in increased doses for 24 to 48 hours prior to operation in an effort to increase liver glycogen, plasma volume and blood pressure. Adrenal cortex extract, 5 c.c. every four hours day and night for 48 hours preceding operation and 10 mg. of desoxycorticosterone acetate, once daily, is a safe routine. Early on the morning of operation, an intravenous infusion of 1000 c.c. of sodium chloride, 0.9 per cent, and glucose, 5 to 10 per cent, is given as well as a supplementary dose of 10 to 15 c.c. of adrenal cortex extract and 10 mg. of desoxycorticosterone acetate. A second infusion of saline and glucose is instituted at the time that the anesthetic is started, and 25 c.c. of adrenal cortex extract are added directly to the infusion. Additional extract is given during the operation if the systolic blood pressure falls below 120 mm. Hg. Epinephrine is given immediately (0.5 c.c.) subcutaneously if the systolic blood pressure falls below 100 mm. Hg. Following operation the patient is treated in a manner similar to that described under "treatment of adrenal crisis." Care should be taken not to give large doses of desoxycorticosterone acetate when the fluid requirement during the postoperative period is being provided by saline and glucose infusions.

Discussion

An analysis of the etiological factors responsible for adrenal cortical insufficiency in this group of 158 patients suggests that the incidence of tuberculosis is appreciably lower than that previously reported. This fact is of significance in relation to the therapeutic response which may be expected, since patients with active tuberculosis or extensive, healed tuberculosis present complications which are not encountered in the non-tuberculous group.

There is no evidence to show that a daily intramuscular injection of synthetic hormone in oil regularly taken is inferior to pellet therapy except in relation to the quantity of hormone which is required. However, the implantation of pellets of crystalline hormone has definite advantages in the treatment of patients who are unable or unwilling to coöperate by continuing daily injections of hormone indefinitely. Sublingual administration of hormone is not practical in most instances because hormone must be taken frequently throughout the day (four to six times daily) and relatively large quantities of hormone are required, hence the cost of therapy is excessively high.

The results of therapy in the present group of patients are striking as judged by survival at 1.5 years and by the extent to which these patients have been rehabilitated. However, it must be pointed out that the present good state of the majority of these patients is the result of intensive therapy with synthetic hormone, supplemented in crisis or during the course of intercurrent infections with adrenal cortex extract therapy and parenteral

TABLE XXVI

Summary of Observations on 64 Patients Treated with Desoxycorticosterone Acetate

Patient	Sex	Age	Occupation	Etiology of Addison's Disease	Duration of Disease (years)	Complications	Blood Pressure		Body Weight		Duration of Hormone Therapy (years)	Carbohydrate Defect	Electroencephalogram	Electrocardiogram	Present Therapy			Present Condition ‡
							*Admission	Present	*Admission	Present					Desoxycorticosterone Acetate	Added Sodium Chloride gm.	Adrenal Cortex Extract	
M. A.	F	48	Housewife	Tuberculous	14.0	Preëxisting hypertension	136/84	133/86	55.0	58.9	0.4	− −	—	"Borderline"	Pellets	3	0	A
I. B.	F	48	Housewife	Non-tuberculous	7.0	Cirrhosis, arthritis	110/74	180/110	48.0	50.0	2.8	0	—	Normal	Pellets	9	0	C
†J. B.	F	38	Housewife	Non-tuberculous	7.0	Rheumatic heart disease	100/70	130/80	53.0	60.0	0.3	+ +	—	—	Pellets	0	0	D
S. B.	M	22	Clerk	Non-tuberculous	3.0	None	100/75	140/80	45.5	56.0	0.7	− −	Abnormal	Normal	Pellets	0	0	A
B. B.	F	53	Housewife	Non-tuberculous	3.0	Arthritis, anemia	90/60	150/100	47.3	42.2	1.3	0	—	"Borderline"	Pellets	0	0	B
W. B.	M	21	Clerk	Non-tuberculous	4.0	Hypothyroidism	92/74	150/112	41.5	50.9	2.6	+ +	Abnormal	Myocardial damage	Pellets	3	0	A
D. W. B.	F	28	Housewife	Non-tuberculous	9.0	None	105/70	118/80	60.0	60.5	2.3	− −	Normal	—	Pellets	0	0	A
†M. B.	F	31	Teacher	Non-tuberculous	5.0	Hypothyroidism, anemia	90/66	102/60	49.4	52.9	1.0	+ + +	—	"Borderline"	Pellets	0	0	D
B. B.	M	22	Salesman	Non-tuberculous	4.0	None	120/76	120/70	56.3	60.5	1.7	+	—	Normal	Pellets	2	0	A
D. B.	M	35	Printer	Non-tuberculous	4.0	Inguinal hernia	108/70	168/98	64.7	68.6	2.9	+ +	—	Normal	Pellets	6	0	A
J. B.	M	56	Engineer	Non-tuberculous	2.0	None	96/82	150/92	60.0	88.6	0.8	− −	—	—	Pellets	2	0	A
W. C.	M	24	Truckdriver	Non-tuberculous	4.0	None	80/50	112/82	50.0	56.0	1.1	+ +	Abnormal	Normal	Pellets	5	0	B
C. C.	F	43	Housewife	Non-tuberculous	4.0	Anxiety neurosis	124/76	118/74	43.1	44.5	2.4	0	—	"Borderline"	Pellets	0	5 c.c.	C
W. J. C.	M	27	Unemployed	Non-tuberculous	8.0	Hypothyroidism	98/60	130/82	64.1	72.8	1.3	+ +	Abnormal	"Borderline"	Pellets	0	0	A
K. D.	F	19	Housewife	Non-tuberculous	2.0	Pregnancy	105/60	115/65	38.8	40.9	1.3	+	Normal	Normal	Pellets	5	0	A
F. D.	M	43	Writer	Non-tuberculous	5.0	None	96/58	108/70	66.8	66.4	3.0	+ +	Abnormal	Normal	Pellets	5	0	B
M. D.	M	29	Clerk	Non-tuberculous	3.0	None	80/60	116/78	50.1	66.6	2.8	+ +	Abnormal	"Borderline"	Pellets	0	0	B
†J. D.	M	68	Unemployed	Non-tuberculous	2.0	Arthritis	108/70	120/80	62.5	69.0	0.2	− −	—	"Borderline"	Percorten	10	0	D
†C. E.	M	67	Mail Carrier	Non-tuberculous	6.0	Arteriosclerosis, senility	104/78	132/78	51.2	48.0	1.7	0	—	"Borderline"	Pellets	8	0	D
Y. E.	F	39	Housewife	Non-tuberculous	4.0	Rheumatic heart disease	102/74	105/65	51.9	56.4	2.6	+ +	—	"Borderline"	Pellets	0	3 c.c.	B
C. F.	M	33	Mechanic	Tuberculous	3.0	Active tuberculosis	90/60	120/80	55.9	68.2	1.2	+ +	Abnormal	Normal	Pellets	0	0	A
J. F.	M	21	Student	Tuberculous	1.0	Active tuberculosis	80/60	140/100	68.2	72.3	0.3	− −	Normal	Normal	Pellets	3	0	B
E. F.	F	49	Housewife	Non-tuberculous	2.0	Arthritis	90/50	142/98	78.2	59.6	1.3	+ +	Normal	"Borderline"	Pellets	3	0	B
R. G.	F	27	Teacher	Non-tuberculous	2.0	Hypothyroidism	107/60	120/80	38.3	46.0	1.5	+ +	Abnormal	Myocardial damage	Pellets	1	0	A
A. H. G.	M	52	Mechanic	Tuberculous	1.0	Healed pulmonary tbc.	105/70	122/76	88.1	87.3	0.3	+ +	Abnormal	Normal	Pellets	0	0	A
F. G.	F	30	Clerk	Non-tuberculous	3.0	None	104/65	110/70	46.8	47.7	2.6	+ +	Normal	"Borderline"	Pellets	5	0	A
A. G.	F	51	Housewife	Tuberculous	6.0	Anemia	116/70	135/78	44.9	54.7	1.2	+	Abnormal	Myocardial damage	Pellets	5	0	A
J. H.	M	22	Clerk	Non-tuberculous	4.0	None	100/60	110/65	63.2	68.2	2.9	0	Abnormal	Normal	Pellets	3	0	A
F. H.	M	24	Clerk	Non-tuberculous	3.0	Splenomegaly	95/54	150/100	59.5	66.4	2.3	+ +	Abnormal	"Borderline"	Pellets	0	5 c.c.	A
A. W. H.	F	20	Housewife	Tuberculous	3.0	Active tuberculosis	108/76	120/88	58.1	59.1	1.8	0	Abnormal	Myocardial damage	Pellets	0	0	A
A. H.	F	40	Housewife	Non-tuberculous	4.0	None	90/60	120/80	45.0	47.3	1.1	0	Normal	"Borderline"	Pellets	3	0	B
I. H.	F	36	Teacher	Tuberculous	5.0	None	108/70	107/70	53.0	53.0	2.3	+ +	Abnormal	Normal	Pellets	0	0	A
A. H. H.	F	38	Housewife	Non-tuberculous	5.0	Splenomegaly	90/58	118/76	40.0	44.9	2.5	+ +	Abnormal	Myocardial damage	Pellets	3	0	B
†H. H.	M	38	Salesman	Non-tuberculous	1.0	None	120/74	120/78	80.5	85.0	0.6	− −	—	Normal	Pellets	0	0	D
C. K.	M	45	Service Mgr.	Tuberculous	7.0	Active tuberculosis	80/60	130/90	65.6	76.0	1.5	+	Abnormal	Myocardial damage	Pellets	0	0	B

TABLE XXVI—*Continued*

Patient	Sex	Age	Occupation	Etiology of Addison's Disease	Duration of Disease (years)	Complications	Blood Pressure		Body Weight		Duration of Hormone Therapy (years)	Carbohydrate Defect	Electroencephalogram	Electrocardiogram	Present Therapy			Present Condition ‡
							*Admission	Present	*Admission	Present					Desoxycorticosterone Acetate	Added Sodium Chloride gm.	Adrenal Cortex Extract	
E. K.	F	47	Stenographer	Tuberculous	8.0	Preëxisting hypertension	190/130	170/110	42.9	44.5	1.2	0	Abnormal	Normal	Pellets	0	0	C
†A. K.	F	32	Housewife	Non-tuberculous	1.0	Puerperal sepsis	90/60	125/80	54.8	59.4	0.2	− −	—	—	Percorten	8	0	D
E. L.	F	51	Bookkeeper	Tuberculous	7.0	None	88/50	136/92	43.5	46.1	1.8	++	Normal	Myocardial damage	Percorten	0	0	C
†M. M.	F	27	Housewife	Non-tuberculous	3.0	None	85/72	120/80	51.3	54.5	2.8	++	—	Myocardial damage	Pellets	10	0	D
F. M.	M	32	Laborer	Non-tuberculous	4.0	Hypothyroidism	92/60	130/80	61.2	62.7	3.2	+++	Normal	Myocardial damage	Pellets	5	0	A
H. M.	M	44	Mechanic	Non-tuberculous	5.0	None	96/54	100/60	66.0	68.2	2.1	− −	Normal	Normal	Pellets	0	0	A
R. M.	F	35	Housewife	Non-tuberculous	4.0	Urticaria	60/40	120/90	49.6	62.7	2.6	+	—	"Borderline"	Pellets	3	0	A
C. N.	F	34	Housewife	Non-tuberculous	5.0	Hypoproteinemia	94/60	110/70	55.9	54.7	3.3	+++	—	Myocardial damage	Pellets	0	0	A
M. N.	F	37	Housewife	Non-tuberculous	2.0	Anemia	90/58	100/84	47.1	42.7	1.0	+	Abnormal	Normal	Pellets	3	0	B
O. O.	M	43	Manager	Tuberculous	11.0	None	88/70	100/80	58.3	63.6	1.8	+	—	Normal	Pellets	4	0	A
M. P.	F	35	Housewife	Non-tuberculous	4.0	Pregnancy	102/80	110/78	71.8	69.3	2.3	0	Normal	Normal	Pellets	3	0	A
A. P.	M	45	Professor	Non-tuberculous	7.0	None	106/76	120/80	72.0	70.0	1.1	+++	Abnormal	"Borderline"	Pellets	0	6 c.c.	A
J. P.	M	19	—	Tuberculous	5.0	Active tuberculosis	85/60	138/92	39.3	47.7	3.3	++	—	Normal	Pellets	0	0	A
S. P.	M	28	Foreman	Non-tuberculous	3.0	None	120/75	130/90	70.9	71.1	2.3	0	—	"Borderline"	Pellets	0	0	A
†O. Q.	M	62	Farmer	Non-tuberculous	2.0	Arthritis, arteriosclerosis	80/62	132/80	50.8	54.7	0.5	−	—	Normal	Pellets	10	0	D
J. S.	M	29	Clerk	Non-tuberculous	5.0	Peptic ulcer	92/70	160/100	55.2	70.7	2.3	−	—	Normal	Pellets	0	0	A
M. S.	F	38	Housewife	Non-tuberculous	3.0	None	80/60	150/106	50.2	58.2	1.3	+	Abnormal	Myocardial damage	Pellets	3	3 c.c.	B
†A. B. S.	M	32	Bookkeeper	Tuberculous	5.0	Active tuberculosis	104/68	146/104	57.4	59.2	1.8	+	—	Normal	Pellets	10	0	D
A. S.	M	40	—	Tuberculous	1.0	Active tuberculosis	80/50	130/80	52.7	52.3	0.3	—	—	Myocardial damage	Pellets	0	0	C
A. C. S.	F	44	Housewife	Non-tuberculous	2.0	Diverticulosis of sigmoid	90/65	115/65	52.7	59.6	2.1	0	—	—	Pellets	0	0	A
H. S.	M	48	Unemployed	Tuberculous	6.0	Active tuberculosis	124/76	138/82	81.0	83.6	1.0	0	Abnormal	Normal	Pellets	6	0	B
A. T.	M	49	Innkeeper	Tuberculous	5.0	Healed pulmonary tbc.	118/80	140/88	60.0	68.2	2.3	++	Abnormal	"Borderline"	Pellets	0	0	B
H. U.	F	34	Housewife	Non-tuberculous	2.0	Rheumatic heart disease	100/50	108/60	40.7	41.0	0.9	+	Abnormal	Myocardial damage	Pellets	4	0	B
†L. V.	F	43	Housewife	Non-tuberculous	2.0	None	100/60	112/75	41.5	43.1	0.2	+	Normal	Myocardial damage	Pellets	0	0	D
E. V.	M	39	Tailor	Non-tuberculous	6.0	None	94/60	118/82	54.4	63.6	3.3	++	Abnormal	"Borderline"	Pellets	0	0	A
P. W.	M	34	Clergyman	Non-tuberculous	9.0	None	95/60	140/90	51.0	58.1	3.3	++	Abnormal	Myocardial damage	Pellets	5	0	B
S. W.	F	55	Housewife	Non-tuberculous	3.0	Arthritis	120/78	158/90	58.5	66.1	2.8	+	Normal	Myocardial damage	Pellets	0	3 c.c.	B
R. W.	M	58	Unemployed	Non-tuberculous	4.0	Coronary occlusion	108/70	122/78	71.2	75.5	2.8	+	—	Myocardial damage	Pellets	7	0	C
B. W.	M	26	Accountant	Non-tuberculous	3.0	Healed pulmonary tbc.	80/60	140/80	57.3	61.4	1.8	0	—	—	Pellets	5	0	A

* Values at the time desoxycorticosterone acetate treatment was instituted or substituted for some other form of therapy.

† Indicates patients who have succumbed. Data for "present weight" and "blood pressure" are the values reported shortly before death. Under "present therapy" are listed the hormone and sodium chloride requirements during the period of survival on desoxycorticosterone acetate therapy.

‡ A = greatly improved. B = improved. C = unimproved. D = dead.

administration of saline and glucose solutions. That the results of therapy are not due primarily to the extract and supplementary sodium chloride therapy is indicated by the mortality rate of 42 per cent which was reported in a group of 34 patients treated with extract and sodium chloride alone (chart 3) and by the fact that at least 60 patients in the present group are receiving only desoxycorticosterone acetate without supplementary sodium chloride or extract therapy.

It is unfortunate that at present commercial adrenal cortex extracts are not assayed for their "carbohydrate-regulating" potency since the benefits to be derived from this factor constitute one of the principal reasons for administering extract to patients in crisis and during the course of intercurrent infections. Furthermore, it has recently been demonstrated [38] that certain adrenal steroids which possess "carbohydrate-regulating" potency actually facilitate sodium and chloride excretion in contrast to the well known sodium and chloride-retaining effect of desoxycorticosterone acetate. It appears probable that a combination of these steroid compounds in correct proportions may not only supplement the deficiency of desoxycorticosterone acetate in respect to "carbohydrate-regulating" potency but may also decrease the tendency for excessive sodium and chloride retention which frequently occurs with rather moderate maintenance doses of desoxycorticosterone acetate.

Studies of electrolyte metabolism, plasma volume, carbohydrate metabolism, electrocardiogram, electroencephalogram, renal, hepatic, muscle and gastrointestinal function emphasize the widespread damage which may occur in patients with adrenal insufficiency. Since many of these changes appear to be irreversible, every effort should be made to establish the diagnosis as early as possible in the course of the disease. Diagnosis of Addison's disease at the time of its onset, however, presents an extremely difficult problem. The use of "deprivation" tests, such as the Cutler-Power-Wilder test,[39] is justified if the patient can be kept in a hospital under very careful supervision. A test described more recently by Robinson, Power and Kepler [40] presents several advantages over the Cutler-Power-Wilder test, and it is certainly advisable to consider applying this test before carrying out procedures which entail much greater risk. Glucose tolerance tests, particularly the response to intravenously administered glucose,[11] and a study of the 17-ketosteroid excretion are of considerable aid.[41] When carefully controlled with adequate periods of placebo medication, we have found the response to sodium chloride and hormone therapy (desoxycorticosterone acetate 2 to 5 mg. daily or adrenal cortex extract, 5 to 10 c.c. daily) to be helpful. More specific, however, is the speed and extent of *relapse which follows the sudden withdrawal of therapy after it has been* maintained for a period of one to two weeks.[42]

Summary

1. One hundred and fifty-eight patients with Addison's disease have been treated with synthetic desoxycorticosterone acetate of whom 148 have re-

ceived subcutaneous implantations of crystalline pellets of synthetic hormone. An analysis of the entire group revealed the following:

(*a*) Tuberculosis appeared to be the etiological factor responsible for the adrenal cortical insufficiency in less than 50 per cent of the patients.
(*b*) Approximately 80 per cent of the total number of cases occurred in patients 20 to 50 years of age.
(*c*) The difference in incidence between sexes was not great, i.e., males 56 per cent.
(*d*) Presenting symptoms were as follows: weakness and fatigability in 100 per cent; increasing pigmentation in 94 per cent; anorexia in 91 per cent.

2. Approximately 90 per cent of the patients required 1 to 5 mg. daily of hormone in oil, injected intramuscularly, or 2 to 10 pellets (125 mg. each) implanted subcutaneously. The average duration of therapy was 1.7 years.

3. The mortality rate for the entire group of 156 patients was 15.4 per cent during the present period of therapy (1.7 years); 46 per cent of the deaths were due to infections and 29 per cent to cardiovascular disease. Sixty of these patients are now receiving desoxycorticosterone acetate treatment alone, 66 patients are receiving synthetic hormone and supplementary sodium chloride medication, and six patients are receiving supplementary daily injections of adrenal cortical extract.

4. A detailed analysis of the results of therapy in 64 patients studied in the Johns Hopkins Hospital revealed that 48, or 75 per cent, of the group were definitely improved, and that 56 per cent of the male patients have now been restored to full time employment. In this group of 64 patients an average gain in weight of 4 kg., and a rise in blood pressure from 100 mm. Hg systolic and 66 mm. diastolic to 126 mm. Hg systolic and 70 mm. diastolic were noted. The effect of synthetic hormone on the abnormal pigmentation was neither striking nor consistent.

5. A high proportion of patients with Addison's disease was observed to show:

(*a*) abnormalities in carbohydrate metabolism (75 per cent).
(*b*) abnormal electrocardiograms (60 per cent).
(*c*) abnormal electroencephalograms (69 per cent).
(*d*) abnormalities in creatine metabolism (69 per cent).
(*e*) reduced hippuric acid excretion (100 per cent).

These abnormalities persisted despite continued desoxycorticosterone acetate, and in certain instances the extent or incidence of the abnormalities increased during the period of therapy.

6. Desoxycorticosterone acetate treatment was followed by transient hypertension (34 per cent), transient edema (27 per cent), circulatory insufficiency (8 per cent), tendon and muscular contractions (4 per cent) and transient peripheral motor paralysis (2 per cent). Practically all

of the over dosage phenomena may be explained on the basis of excessive retention of sodium and chloride. For this reason the dose of supplementary sodium chloride medication, if used at all in conjunction with desoxycorticosterone acetate, must be regulated carefully. A diet of low potassium content is definitely contraindicated in patients under treatment with desoxycorticosterone acetate. The incidence of undesirable complications may be reduced greatly by care in the regulation of the dose of synthetic hormone and by an appreciation of the mechanism by which complications are initiated.

Conclusion

The use of desoxycorticosterone acetate in the treatment of a large group of patients with Addison's disease has been associated with the rehabilitation of approximately 50 per cent of the patients. A striking reduction in mortality rate was observed at the end of 1.5 years of therapy. The disturbances in function which may persist despite desoxycorticosterone acetate therapy have been indicated and the undesirable effects of excessive doses of synthetic hormone have been described. If reasonable care is employed in regulating the dose of hormone, complications resulting from overdosage may be greatly reduced. The functional changes which develop in the heart, brain, liver, kidney, muscle, gastrointestinal tract and skin of patients with long-standing adrenal cortical deficiency demonstrate the protean nature of the disease and indicate the great need for early diagnosis.

Acknowledgments

This report would not have been possible without the continued coöperation of a large group of physicians who were kind enough to provide us with information relating to the hormone assay, implantation of pellets and subsequent clinical course of patients under their care. We also wish to acknowledge the assistance of Miss Rachel Fee, nurse in charge of the metabolism unit, Miss Janet Ruth Engebretson, dietitian-in-charge, and Drs. Marshall Clinton, Jr., and John Arthur Luetscher, Jr. We are indebted to Dr. Warfield M. Firor, Associate Professor of Surgery, for implanting pellets in the patients who were studied in the Johns Hopkins Hospital.

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PRIMARY SPLENIC NEUTROPENIA; A NEWLY RECOGNIZED SYNDROME, CLOSELY RELATED TO CONGENITAL HEMOLYTIC ICTERUS AND ESSENTIAL THROMBOCYTOPENIC PURPURA *

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THE spleen may no longer be regarded as an organ of complete mystery. Out of ancient and modern superstitious musings and the obscurity of an incomplete, controversial and largely hypothetical pathologic hematology have gradually emerged sufficient facts relating to splenic structure and functions to compare favorably with current knowledge of the other abdominal viscera. The pioneer work of Barcroft, McNee, Lord Dawson, and Krumbhaar, in creating sound fundamental concepts of physiologic splenic functions has been supplemented by thorough controlled studies of human pathologic splenic diseases, with improved technics by the clinical hematologists, Kaznelson, Frank, Dameshek, Doan and Wiseman among others. Not only practical advances in the treatment of well established splenic syndromes but also recognition of previously unsuspected entities have inevitably followed. The present communication reports what is believed to be a hitherto unrecognized cause of neutropenia, resulting from a pathologically altered, physiologic function of the normal spleen.

Anatomically, the spleen may be regarded as consisting of three structures: (1) the reticulo-endothelial system, (2) the lymphatic component and (3) the vascular spaces. Each of these plays a definite rôle in the physiology of the mammalian organism as a whole. There are, of course, in common with other tissue structures, still some obvious gaps in our knowledge, but none the less, some of the more important of these physiologic activities of the spleen are now well established. Chart 1 presents a diagrammatic summarization of the generally accepted functions together with current concepts corresponding to the abnormalities characteristic of and related to certain clinical diseases.

The essential phagocytic activity of the cells of the reticuloendothelial system for red and white blood cells, platelets, bacteria and other foreign particulate matter has long been known and may be readily observed in any laboratory in which the study of fresh tissues supravitally stained is undertaken. Any intensification of this physiologic phagocytosis of other cells *may produce* a pathologic disequilibrium characterized by a sharp diminution in one or more of the circulating elements in the blood. Whether the splenic phagocytes increase in number and destructive activity through abnormal hereditary or environmental stimuli, or whether they respond secondarily to fundamental alterations in the blood elements themselves, which

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render them more readily phagocytized, is not proved. Whatever the mechanism and however exerted, the fact remains that excessive erythrocyte destruction occurs in congenital hemolytic icterus and abnormal platelet se-

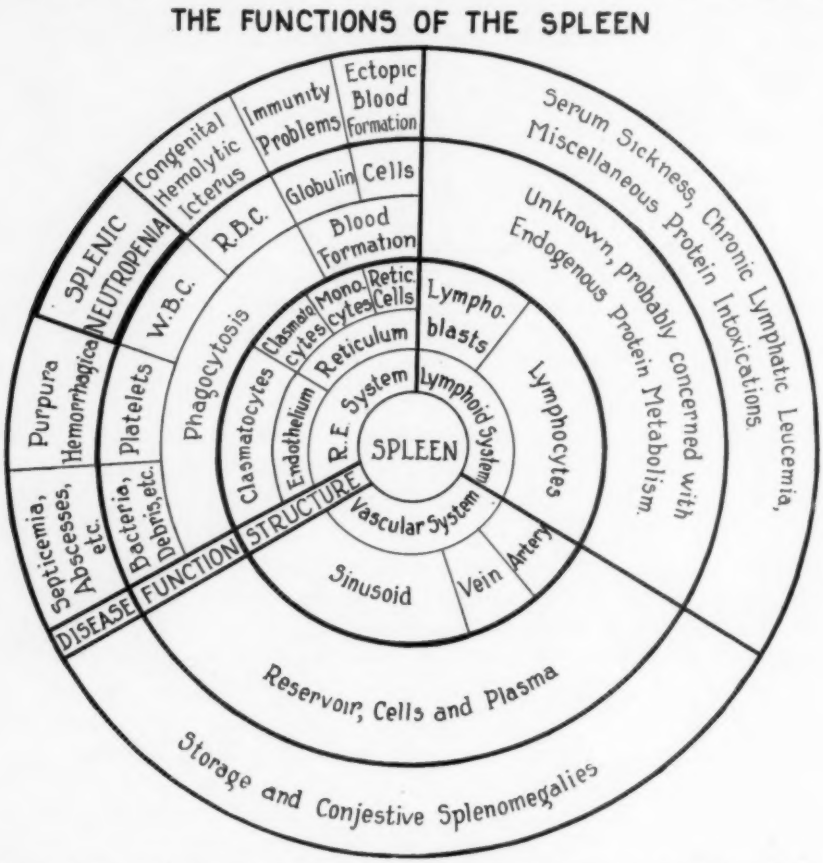

CHART 1. The functions of the spleen. This diagram is drawn to show the relationships between structural elements of the spleen and their physiologic functions. Added to this in the outermost circle are shown certain pathologic states that may result from alteration of these physiologic functions. The inner circle is represented by the structural components of the spleen. Arranged in radial fashion from each of these units is placed the corresponding function of each element. For example, the reticulo-endothelial component of the spleen consists of endothelium and reticulum cells; from the former are derived clasmatocytes, and from the latter clasmatocytes, monocytes and daughter reticulum cells. The clasmatocytes (chiefly) but also the monocytes dispose of effete cellular elements and foreign substances by phagocytosis (next to outer circle). A disturbance (pathologic increase) in this function when directed principally against the neutrophilic leukocytes may result in severe neutropenia (the splenic neutropenia of the outermost circle); when the accelerated phagocytosis is directed against other elements, the other diseases shown may result.

questration in essential thrombocytopenic purpura, both of which may be corrected completely by successful splenectomy.

On theoretical grounds alone, and by analogy, a similar overactivity of the splenic macrophages for granulocytes was predicted, and the first cases reported from this clinic at Atlantic City in May 1939.[1] This syndrome

has since been recognized, confirmed, and reported from two other clinics.[2, 3] The following discussion is the first detailed account of the extended and prolonged observations of the original patients with this granulocytopenic syndrome, after sufficient time may be presumed to have elapsed for any further hematologic or other organic diseases to make their appearance if they were going to develop. Because of the unique nature of this disturbance and certain inevitable and characteristic variations from patient to patient, each case will be presented in some detail.

Case Reports

Case 1. J. M. S.,* female, aged 38; final diagnosis: *acute* splenic neutropenia. This patient had been in normal health until October 4, 1938, ten days before admission to the University Hospital. The first symptoms were interpreted as a mild coryza, self treatment for which consisted of amphetrine by inhalation, nose drops (Vicks) and one aspirin tablet. Eight days later her throat became sore and she was seen by her family physician for the first time. A blood count was taken and a marked leukopenia (1900 per cu. mm.) with only 14 per cent neutrophiles was found. She was seen in consultation on the same day by one of us (B. K. W.) who made the following observations in the home: temperature 102, pulse 98, respirations 20. The throat was diffusely red and there was an ulcerated area on the mucosa of the right posterior pharynx about one half cm. in diameter. There was a slight generalized lymphadenopathy and the spleen was felt at the left costal border during quiet respirations, descending approximately two cm. upon deep inspiration. A purpuric area of spontaneous origin was found on the right lateral aspect of the thigh. The peripheral blood showed 1,400 white cells per cu. mm. with only 10 per cent neutrophiles, monocytes and lymphocytes being about equally represented. No pathologic qualitative changes in the white blood cells were seen. Sternal bone marrow aspiration in the home showed no foreign cell infiltration or toxic hypoplasia, but unexpectedly revealed a marked *hyperplasia* of myeloid cells without appreciable "shift to the left," the majority being mature polymorphonuclears and myelocytes "C." The diagnosis was not immediately evident, and suspecting a type of blood dyscrasia not previously observed in this clinic, hospitalization was advised for further study.

Upon admission to the hospital the next day, October 14, additional historical facts were elicited as follows: The patient was of American parentage and had always been in average good health. There had been "growing pains" in childhood without actual swollen or painful joints. Ten years prior to the present admission, however, there had been a chronic recurring mild sinusitis accompanied by painful swelling of most of the larger, as well as some of the smaller joints, but not the spine. The involvement had been migratory in character, but whether these symptoms reflected acute rheumatic fever or rheumatoid arthritis could not be determined. During the eight months preceding the present illness, these symptoms had been entirely absent. A tonsillectomy had been performed in 1926, and there was a miscarriage with curettage in 1932. There was a full term pregnancy with spontaneous delivery of a normal infant six months before the beginning of the present illness. A blood count done in the hospital at that time was reported as normal. The best weight of the patient had been 154 lbs., average weight 138 and present weight 144. A detailed inquiry into the possible ingestion of drugs revealed no additional facts. There was no individual or family history of allergic manifestations. Other routine historical data were not pertinent to the present illness.

* This patient was referred by Dr. H. K. Mouser, of Marion, Ohio, whose cordial cooperation made possible the subsequent studies of this first case identified as splenic neutropenia.

The physical examination of the patient in the hospital revealed no new signs. The temperature was 102.8°, pulse 118, respirations 22, blood pressure, systolic 110, diastolic 80. The laboratory examinations other than the blood (see chart 2) were

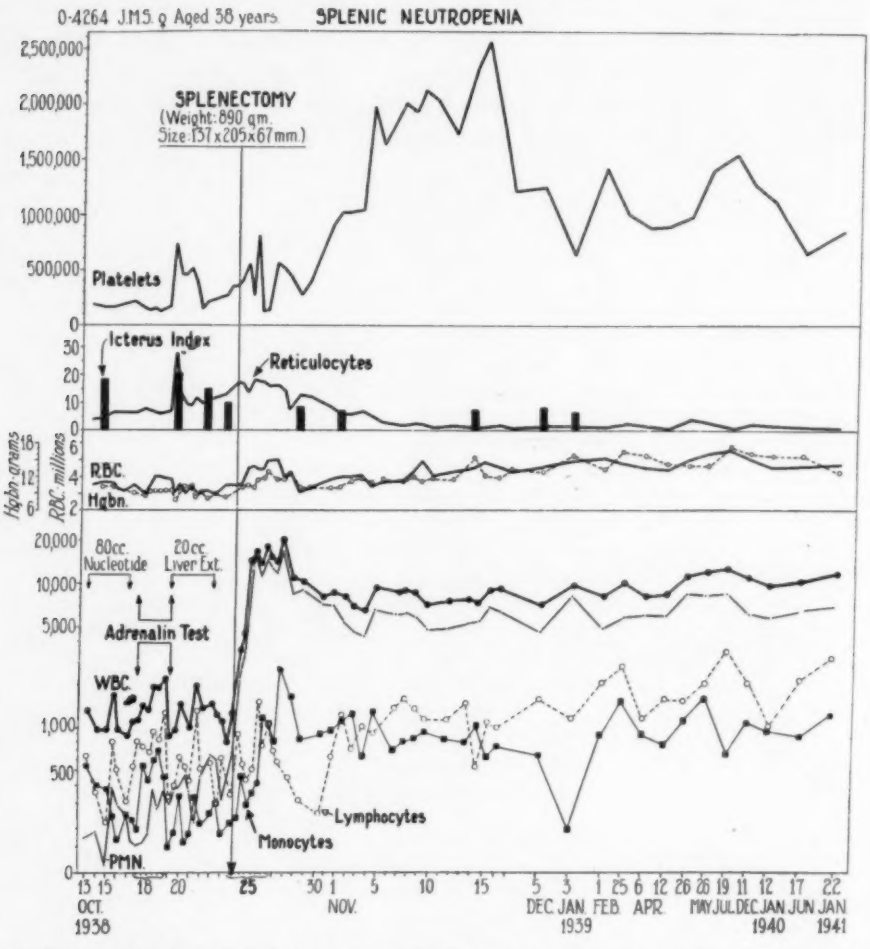

CHART 2. The hematologic data in case 1 before and after splenectomy. The charting of the white blood cells is upon a semi-logarithmic scale. The marked neutropenia, mild thrombocytopenia, and anemia with slight icterus and reticulocytosis are shown to be completely and permanently corrected by the splenectomy of October 25, 1938. The immediate rise in neutrophiles on the day of operation is especially noteworthy and characteristic.

of negative rather than positive diagnostic significance. Five urinalyses gave normal chemical and microscopic findings; Wassermann and Kahn reactions were negative; agglutination tests for typhoid, paratyphoid and undulant fever were negative; repeated blood cultures yielded no growth; all blood chemical determinations were normal; liver function test (hippuric acid) was within normal limits; stereoscopic roentgen-ray films of the chest showed mild bronchiectasis at the left base; roentgen-rays of teeth revealed no root abscesses; roentgen-ray films of the sinuses were clear and cultures yielded no pathogenic organisms. A second sternal puncture reaffirmed the essential integrity of the bone marrow for myeloid elements as recorded in table 1.

TABLE I
Supplement to Chart 2

	Detail of Blood Examinations					Details of Sternal Bone Marrow Examinations	
	Oct. 14, 1938	Oct. 25, 1938		Dec. 5, 1938	Jan. 22, 1941	Oct. 17, 1938	
	Admission to Hospital	½ h. before Splenectomy	8 h. after Splenectomy	1 mo. 5 days after Splenectomy	2 yrs. 2 mos. after Splenectomy	8 days before Splenectomy	
Total W.B.C.	1,000	1,400	20,000	8,150	11,200	Myeloid Elements	
Total R.B.C.	3,710,000	3,650,000	5,030,000	4,680,000	4,870,000	PMN Mature	31
Total Platelets	178,000	350,000	140,800	1,263,000	876,000	Metamyelocytes	12½
Hemoglobin (Gm.)	10.4	10.3	13.0	13.0	13.5	Myelocyte "C"	32
Reticulocytes (%)	4.6	17.6	16.0	1.4	0.8	Myelocyte "B"	14½
Cell Volume R.B.C. (%)	30	30		47	47 *	Myelocyte "A"	2
Sedimentation Index (R.B.C.) (mm./min.)	1.2	1.4		0.8	0.1 *	Myeloblasts	1
Icterus Index	18.6	10		8.0	4 *	PME Myelocyte C	1
Van den Bergh						Lymphocytes	3
Differential Count (%)				—		Reticulum Cells	½
PMN—Mature	12	52	77	65	61	Plasma Cells	½
Metamyelocytes	4	2	6	0	0	Monocytes	2
Myelocyte "C"	4	2	4	0	0	R.B.C. (No. per 100 W.B.C.)	
Myelocyte "B"	0	0	3	0	0	Normoblasts	27
Eosinophiles	0	2	0	4	1	Late Erythroblasts	6
Lymphocytes	36	26	4	22	27	Early Erythroblasts	2
Monocytes	40	16	6	9	11	W.B.C. : R.B.C. Ratio	5 : 1
Normoblasts No. per 100 W.B.C.	0	1	0	0	0		
Fragility R.B.C.	.412–.300	.412–.300				Remarks: Megakaryocytes normal. Marrow shows no pathologic elements. Grossly and microscopically shows hyperplasia.	

* Date January 12, 1940.

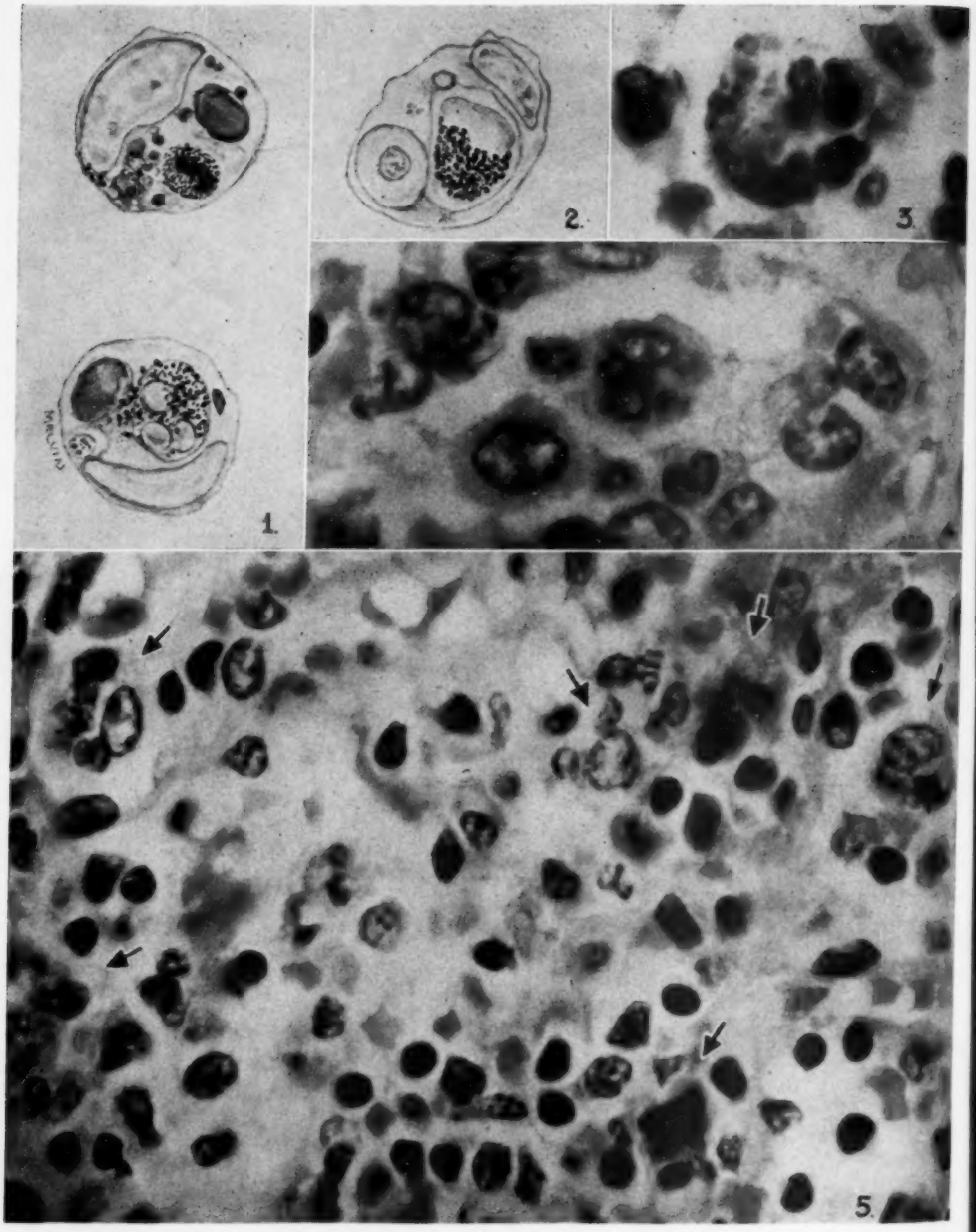

PLATE 1. *Fig. 1.* A drawing of two highly phagocytic clasmatocytes as viewed in supravitally stained scrapings of the pulp from the spleen through the oil immersion lens of the microscope. The material was obtained from case 3. The uppermost cell shows the phagocytosis of a single whole red blood cell, numerous fragmented particles of red blood cells, and a stab type of neutrophile. The lower clasmatocyte contains a three lobed neutrophile, a whole red blood cell and just above the left pole of the nucleus of the phagocyte a mass of platelet cytoplasm that has not yet completely disintegrated.

Fig. 2. A drawing of a clasmatocyte from the same source as figure 1 showing phagocytosis of a myelocyte "C" and a normoblast.

Attempts to treat the persistent leukopenia medically with parenteral administration of pentnucleotides (0.7 gm. every six hours for eight doses), and liver extract (100 units every 12 hours for four doses) were without any demonstrable influence on the white blood cell count or the clinical picture. An adrenalin test showed a small increase of neutrophiles from 200 to 350 per cu. mm. which was not deemed significant.

Inasmuch as the patient continued to show a steadily progressive, non-remitting clinical course, with rising temperature (103.5°), enlarging spleen (now 5 cm. below the left costal border during quiet respiration), increasing angina and profound granulopenic leukopenia, further delay was considered unsafe, and splenectomy was advised and accomplished on October 25, 1938 by Dr. George Curtis. An immediate rise in leukocytes occurred post-splenectomy, and after seven hours the peripheral blood showed 20,100 white blood cells, of which 90 per cent were mature, motile neutrophilic granulocytes (see table 1). The subsequent readjustment of the white cells, the over compensatory peak in platelets, and the reëstablishment of reticulocytes, red blood cells and icterus at normal levels are shown on chart 2. The patient made a good clinical recovery with only one complication, cystitis of the colon bacillus type, occurring on the tenth day post-operative, which cleared up promptly under mandelic acid treatment. She was discharged on the twenty-first post-operative day. As indicated on the chart, she has been seen frequently since, but no return of the granulopenia has occurred, nor have evidences of leukemia or any other disease appeared to date (June 1942).

At operation, the liver appeared normal, and no evidence of portal hypertension was apparent. The removed spleen weighed 890 gm. and from it 241 gm. of blood could be expressed. The entire peritoneal surface was smooth and there were no adhesions. The elongated organ was a dull muscular red. There was no thickening of the capsule. Scrapings of the pulp substance stained supravitally showed a marked increase in the phagocytic clasmatocytes, often 10 or more to an oil immersion field, within which ingested neutrophilic leukocytes predominated with also some mature red blood cells and an occasional normoblast. No other abnormalities of the spleen were determined either supravitally or upon study of the fixed sections. Plate 1, figures 3 and 5 are photomicrographs of the phagocytic phenomena observed.

*Case 2.** B. K., male, aged 50; final diagnosis, *subacute* splenic neutropenia. This patient was admitted to the University Hospital for the first time on September 21, 1938 with the presenting complaint of progressive fatigue. His present illness began two months previously, when his family physician in another city promptly referred him to a hospital for diagnosis. After some 17 days of observation and investigative studies no conclusion was reached, and the patient was discharged after receiving two blood transfusions. He was then admitted to University Hospital where the following studies were directed by one of us (B. K. W.). The patient was a poultry dealer of Jewish extraction who had always been in good health until the

* Referred by Drs. B. S. Kline and S. F. Rosen, Cleveland, Ohio, whose coöperation we gratefully acknowledge.

Fig. 3. Photograph of a highly phagocytic clasmatocyte from the spleen of case 1. Oil immersion lens and hematoxylin-eosin stained paraffin section. Magnification to correspond approximately with drawings of figures 1 and 2.

Fig. 4. A photograph through the oil immersion lens of a phagocytic clasmatocyte from the spleen of case 2. Hematoxylin-eosin stained paraffin section. Magnification approximately upon the scale of the drawings shown as figures 1 and 2.

Fig. 5. A photograph of an oil immersion field (× 1250) selected from a paraffin section of the spleen of case 1. At least six highly phagocytic clasmatocytes (indicated by the arrows) were present in this single field, illustrating the marked increase in number and activity of these cells. The illustration is typical of the density of concentration of the macrophages found in the spleen of this case. Hematoxylin-eosin stain.

advent of symptoms of exhaustion as noted. He had never been exposed to coal tar products, lead or other industrial hazards. He had taken no drugs except aspirin in small quantity. There was no history of allergy or blood diseases in either the patient or his family. Interrogation by systems revealed no relevant data. Physical examination showed as the only significant positive finding an enlarged spleen, extending 6 cm. below the costal border in the mid-clavicular line. The laboratory studies gave the following data: Blood showed marked leukopenia, moderate anemia and thrombocytopenia, and the bone marrow showed myeloid hyperplasia (see table 2); Wassermann and Kahn reactions were negative; urinalysis was negative; hippuric acid and bromsulphalein tests for liver function were within physiologic limits; all blood chemical determinations were normal; basal metabolic rate was +9 per cent; stool examinations were negative for occult blood, ova and parasites; gastric analysis showed 1° of free acid in the fasting sample rising steadily to 72° in a specimen 60 minutes after histamine; fluoroscopy of the stomach and colon, and a chest roentgen-ray plate revealed no organic pathologic lesions referable to these areas. The patient remained in the hospital for three days during which the temperature, pulse and respirations were normal. The adrenalin test was positive for excessive splenic sequestration (chart 3). Congenital hemolytic jaundice, hypoplastic anemia and Banti's syndrome were ruled out, but no positive diagnosis could be decided upon, and he was discharged with the request to return for further observations.

Seven weeks later the same patient was re-admitted to the University Hospital. The interval history recorded a steadily increasing weakness and an enlarging tumor mass in the abdomen. Upon physical examination the patient was now found to be clinically jaundiced and the spleen extended 8 cm. below the left costal border. The

TABLE II

Supplement to Chart 3

	Details of Blood Examinations					
	Sept. 21, 1938	Nov. 8, 1938	Nov. 18, 1938		Dec. 19, 1938	Oct. 27, 1939
	1st Adm. to Hosp.	2nd Adm. to Hosp.	½ Hour before Splenectomy	8 Hours after Splenectomy	1 Month, 1 Day after Splenectomy	11 Months, 3 Weeks after Splenectomy
Total W.B.C.	1,850	1,200	1,000	12,600	4,100	8,500
Total R.B.C.	3,320,000	2,480,000	2,650,000	3,460,000	4,120,000	5,110,000
Total Platelets	185,920	69,440	29,440	560,000	799,280	1,522,780
Hemoglobin (Gm)	10.6	7.5	7.6	10.0	13.0	13.9
Reticulocytes (%)	14.2	12.0	28.0	22.6	0.6	2.2
Cell Volume R.B.C. (%)	32	27	—	—	41	48.5
Sedimentation Index mm./min. R.B.C.	1.7	0.6	—	—	1.4	1.0
Icterus Index	7	20	—	—	7	7
Differential Count						
PMN—Mature	26	24	12	85	34	50
Metamyelocytes	0	2	6	0	0	0
Myelocyte "C"	0	2	0	0	0	0
Myelocyte "B"	0	0	0	0	0	0
Eosinophiles	16	6	2	0	10	1
Basophiles	6	0	0	0	3	0
Lymphocytes	40	44	62	1	36	35
Monocytes	12	22	18	14	17	14
Normoblasts No. per 100 W.B.C.	0	0	0	0	0	0
Fragility R.B.C.	.471–.319	.430–.300	—	—	.430–.300	.380–.282

TABLE II (*Continued*)

	Details of Sternal Bone Marrow Examination			
	Sept. 21, 1938	Nov. 8, 1938	Dec. 14, 1938	April 5, 1939
	1st Admission to Hospital	2nd Admission to Hospital	26 days—Post Splenectomy	4 Mos. 17 days—Post Splenectomy
Myeloid Elements				
PMN Mature	38	19	39.5	58
Myelocytes "C"	36.5	56	28.5	24
Myelocytes "B"	4.0	8	3.0	2
Myelocytes "A"	0	0	1.0	0
Myeloblasts	0	0	0.5	0
B.M.B.	0.5	0	1.0	0
PME Mature	3.5	3.5	2.0	2
PME Myelocytes "C"	6	0	1.0	2.5
PME Myelocytes "B"	0.5	0	0	1.0
Lymphocytes	4.5	4.5	11.0	6.0
R.E. Cells	0.5	1.0	0	0
Plasma Cells	3.0	3.0	2	2
Monocytes	0.5	3.0	9	1.5
Clasmatocytes	0.5	1.0	1	1.0
RBC (No. per 100 WBC)				
Normoblasts	119	98	46	35
Late Erythroblasts	99	8	2	5
Early Erythroblasts	18	5	3	1
Megakaryocytes	1	0	0.5	0
WBC : RBC Ratio	1 : 2.36	1 : 1.1	2 : 1.1	3 : 1.2
Remarks:	No. Path. Cells seen.			

neutropenia, the hemolytic anemia and thrombocytopenia had become more severe (see table 2 and chart 3) and the bone marrow more hyperplastic, so that it seemed clear that the enlarged spleen was the responsible agent. A diagnosis of splenic neutropenia was made and splenectomy was successfully accomplished on November 18, 1938, by Dr. G. M. Curtis with hematologic and clinical results entirely comparable with those already noted in case 1. (See chart 3.) The liver appeared normal at operation, and there were no evidences of portal hypertension. The spleen closely resembled grossly and microscopically that of case 1. No abnormality could be determined except the excessive phagocytosis of neutrophilic leukocytes and erythrocytes, which was most strikingly seen in the supravitally stained scrapings of the splenic pulp, as illustrated on plate 1, figure 4. The patient developed severe abdominal pain in the left upper mid-abdomen on the third post-operative day, which persisted for 10 days and was thought to be due to splenic vein thrombosis although the exact nature of this temporary abdominal distress was never proved. The patient was discharged to his home on December 19, 1938, with all blood elements essentially normal (table 2). Repeated follow-up observations have shown no return of the original or of any other blood dyscrasia, and this man has continued in normally good health throughout the past 3½ years.

*Case 3.** L. B., female, aged 67; final diagnosis: *chronic* splenic neutropenia. This patient was admitted for the first time to the University Hospital on October 21, 1937, with the chief complaint of progressive weakness during the past four months. She was subjected to a diagnostic study by one of us (C. A. D.) and the following facts were obtained: The history revealed that the patient had been in usual health

*Referred by Dr. Mark D. Godfrey, Columbus, Ohio, whose coöperation we gratefully acknowledge.

until the spring of 1937 when she noted some slight diminution in energy. The degree of exhaustion gradually increased until by September she was forced to spend the greater portion of her time in bed. She was given iron for anemia by her local physician, but became nauseated and discontinued it. Seen later by another physician, the leukopenia was found and 10 doses of pentnucleotide of 10 c.c. each were given with no improvement. No other drugs were taken. She had had a mild but persistent,

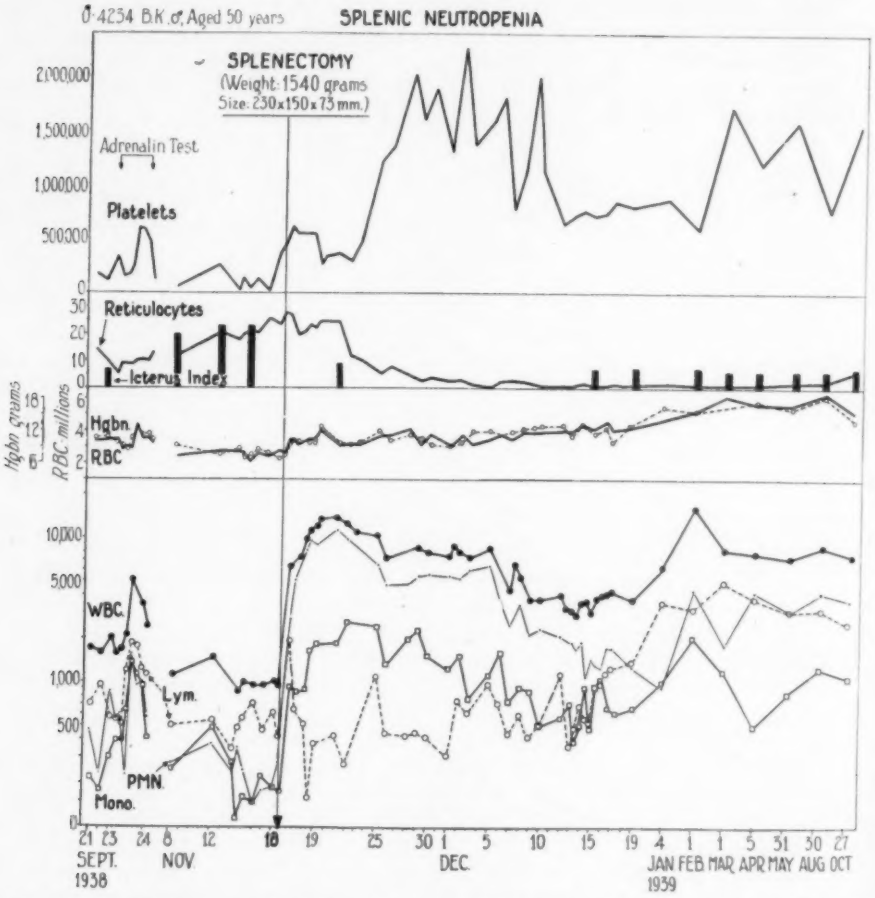

CHART 3. The hematologic findings in case 2 before and after splenectomy. The white cells are charted upon a semi-logarithmic scale. The break in the lines from September 24, 1938, to November 8, 1938, represents a period in which the patient was out of the hospital and blood studies were not obtained. The immediacy of the results after the removal of the spleen is clearly shown. Corrections in levels of red cells, icterus, reticulocytes, and platelets are also apparent. This patient really exhibited a hypersplenism directed toward all the circulating blood elements but chiefly toward the granulocytes.

chronic, non-productive cough "all her life." For the previous seven years there had been from time to time some tenderness and swelling of various joints, chiefly the fingers, but these symptoms had been absent for two months prior to admission. No other relevant data were elicited. The physical examination showed nothing unusual for a person of this age except an enlarged hard spleen extending 8 cm. below the costal border. The leukopenia (650) was the most profound we had ever encountered,

with the sternal marrow hyperplastic (see table 3, and chart 4). Urinalysis was within normal limits; phenolsulphonphthalein kidney function test was within normal limits. Liver function tests: bromsulphalein excretion was normal, and hippuric acid test showed excretion of 2.36 grams in two hours. All blood chemical determinations were normal; glucose tolerance test showed mild diabetic type of curve; electrocardiogram revealed marked myocardial damage; chest roentgen-ray plate showed diffuse fibrosis with an oval area on the right side that was interpreted as a thickening of the pleura, probably the result of an old healed empyema; fluoroscopy of the stomach and colon showed no organic pathology. A Banti's syndrome was suspected and splenectomy was advised, but refused by patient and family because of age and the apparently great surgical risk. Before discharge the patient was given 12 c.c. of liver extract over a period of 10 days without any improvement.

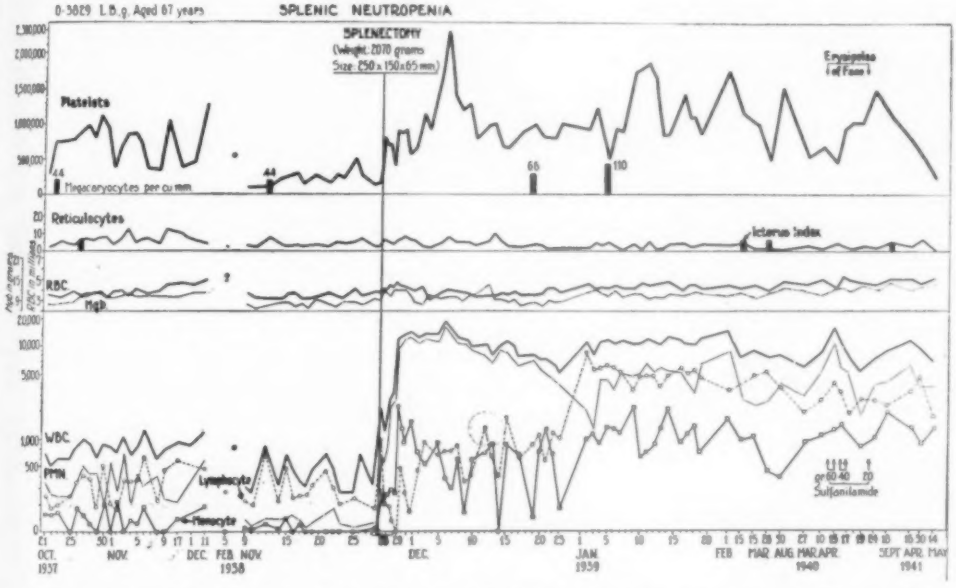

CHART 4. The hematologic data, case 3, before and after splenectomy. The period from December 1, 1937, to November 9, 1938, represents the interval between the first and second admissions to the hospital. The granular cells were almost completely absent from the peripheral blood prior to splenectomy during the second hospital admission. Sixteen months following splenectomy during which time permanent correction of the neutropenia was observed, the patient suffered an attack of facial erysipelas. The customary neutrophilic leukocytosis incident to this disease is well shown on this chart, prompt recovery following sulfanilamide therapy. Only the white cells are charted upon a semi-logarithmic scale.

Approximately one year later, November 9, 1938, this patient was again brought to the clinic and re-admitted to the Research Service. During the interim she had become increasingly weaker, more dyspneic, and had developed a purulent conjunctivitis. An ulceration had appeared two months earlier on the right lower leg from an abrasion of the skin, which gradually spread, failing to respond to any treatment. When examined in the hospital, the ulcer crater measured 5½ cm. in diameter by ½ cm. deep. The spleen of this patient had continued to enlarge until it was found to extend deep into the left pelvis inferiorly. No lymphadenopathy was apparent. The blood examination showed a still more profound leukopenia (150), there being only 25 to 30 neutrophilic leukocytes per cu. mm. of blood. There was also a more definite

thrombocytopenia with red cells, hemoglobin and reticulocytes relatively unchanged. There was no jaundice. An examination of the sternal bone marrow showed a maintained hyperplasia of the myeloid elements, mostly at the myelocyte "C" level (see table 3). The lowest circulating granulocyte level occurred on November 18 at which time only 1 per cent neutrophiles were found in a total white cell count of 300 per cu. mm. The highest value was recorded on November 16, 25 per cent neutrophiles in a total count of 450 white blood cells. Other pertinent laboratory studies were as follows: Liver function tests showed 2.63 gm. hippuric acid excreted, galactose tolerance test showed no galactose excreted, no bromsulphalein dye (5 mg. per kilo) was found in circulation at end of 30 minutes. The total serum proteins were 6.1 per cent; serum calcium 10.2 mg. per cent. The basal metabolism was +26 per cent. The phenolsulphonphthalein kidney function test showed a dye excretion of 60 per cent in two hours, with urinalysis normal. The temperature during the 19 days in the hospital before splenectomy varied between 97.8° and 101.4° F. Symptomatic therapy was of no benefit, and at this time both patient and family asked for splenectomy.

Splenectomy was accomplished on November 28, 1938, by Dr. G. M. Curtis. There was no free fluid in the abdominal cavity nor any evidence of venous engorgement. The liver was normal in size and appearance. The spleen was freely movable with no adhesions and, when removed, weighed 2,070 gm. In addition, a large accessory spleen, measuring 2 by 2 by 1½ cm., was extirpated. Supravitally stained scrapings of the pulp of the spleen showed a marked increase in phagocytic clasmatocytes or macrophages, most of which were actively destroying neutrophilic leukocytes (see plate 1, figures 1 and 2). Exactly 35 minutes after the splenic pedicle had been

TABLE III

Supplement to Chart 4

	Details of Blood Examination					
	Oct. 21, 1937	Nov. 9, 1938	Nov. 28, 1938		Jan. 2, 1939	May 14, 1941
	1st Admission to Hospital	2nd Admission to Hospital	½ h. before Splenectomy	8 h. after Splenectomy	1 mo. 3 days after Splenectomy	2 yrs. 5½ mos. after Splenectomy
Total W.B.C.	650	150	300	3,300	11,450	6,300
Total R.B.C.	3,690,000	3,600,000	3,790,000	4,600,000	4,570,000	4,810,000
Total Platelets	310,000	79,200	151,600	892,000	914,000	230,000
Hemoglobin (Gm.)	8.5	8.0	9.4	11.8	11.1	13.9
Reticulocytes (%)	2.8	3.0	2.8	5.2	1.4	0.4
Cell Volume, R.B.C. (%)	30	—	—	36	38	—
Sedimentation Index mm./min. R.B.C.	0.9	—	—	1.0	0.6	—
Icterus Index	6.6	—		—	—	—
Differential Count						
PMN—Mature	48	20	15	84	18	54
Metamyelocyte	2	5	5	6	0	0
Myelocytes "C"	0	0	0	0	0	0
Myelocytes "B"	0	0	0	0	0	0
Eosinophiles	2	0	0	0	0	0
Basophiles	0	0	0	0	0	0
Lymphocytes	32	70	70	2	73	26
Monocytes	16	5	10	8	9	20
Normoblasts (No. per 100 W.B.C.)	0	0	0	0	0	0
Fragility R.B.C.	.412–.300	—	—	—	—	—

TABLE III (*Continued*)

	Details of Sternal Bone Marrow Examination		
	Oct. 21, 1937 1st Admission to Hospital	Nov. 15, 1938 2nd Admission to Hospital	Jan. 5, 1939 1 mo. 7 days after Splenectomy
Myeloid Elements			
PMN Mature	2.5	0	2.0
Myelocytes "C"	59.0	92.5	80.0
Myelocytes "B"	20.5	1.0	4.5
Myelocytes "A"	2.5	0	0.5
Myeloblasts	0	0	0
P.M.B.	1.5	1	0.5
P.M.E. Mature	1.5	2.0	0
P.M.E. Myelocytes "C"	4.5	2.0	2.5
P.M.E. Myelocytes "B"	0.5	0	0
Lymphocytes	5.0	0	5.5
R. E. Cells	0	0	0
Monocytes	0.5	0	0.5
Plasma Cells	2.0	0.5	1.0
Clasmatocytes	0	0	0.5
R.B.C. (No. per 100 W.B.C.)			
Normoblasts	17	23	64
Late Erythroblasts	5.5	21	19
Early Erythroblasts	2.5	17	1
Megakaryocytes	0	1.0	2.5
W.B.C. : R.B.C. Ratio	4 : 1	2 : 1.2	2 : 1.6

clamped the white blood count was 2,250 with 32 per cent neutrophiles; six hours post-splenectomy the white blood cells were 3,350 with 84 per cent of the cells neutrophilic leukocytes; 24 hours later the white blood count was 11,850 with 78 per cent neutrophiles. The post-operative course was uneventful, without any complications, and it was interesting to note that the chronic ulceration of the right leg healed even before the abdominal incision. In April 1940, this patient, now 70 years of age, suddenly developed an acute fulminant erysipelas of the face, and was admitted to the University Hospital on the third day of her illness with a high fever and semi-comatose. Sulfanilamide was given in the dosage indicated on chart 3 with immediate improvement and prompt recovery. The leukocytic reaction was a characteristic and adequate response to infection, completely substantiating the fundamental integrity of the bone marrow in this patient. She has continued well to the present time (January 1942).

Case 4. T. V., female, aged 12; final diagnosis: *subacute* splenic neutropenia and thrombocytopenia (chart 5). This girl was admitted to the Research Service, University Hospital, May 6, 1941, where the studies were directed by one of us (C.A.D.). The chief complaints were anorexia, weakness, persistent low grade fever, frequent epistaxes, bleeding gums, and generalized ecchymoses and petechiae of skin and mucous membranes. The patient had been in usual health until February 5, 1941, when she became ill with what was diagnosed as "influenza and bronchitis with sore throat and enlarged cervical lymph glands." One week after the initial onset, small subcutaneous ecchymoses appeared first on the arms and subsequently in "crops" over the entire body, which phenomenon continued up to and including the time of admission. Some 20 epistaxes were reported, the last having continued for 24 hours just prior to entering the hospital. A "diarrhea" of four to five "tarry" stools daily had persisted for two weeks, with a weight loss only from 74 to 71 lbs. The patient is said by the mother never to have been physically strong or rugged, having suffered more or less severely from all childhood diseases, and having always "bruised easily."

Family history was non-contributory for blood dyscrasias. The significant physical findings on admission were: temperature 100° F., pulse 88, respirations 24, blood pressure systolic 114, diastolic 60; pallor of skin and mucous membranes with numerous petechial hemorrhages scattered over chest, abdomen, back and extremities, and large

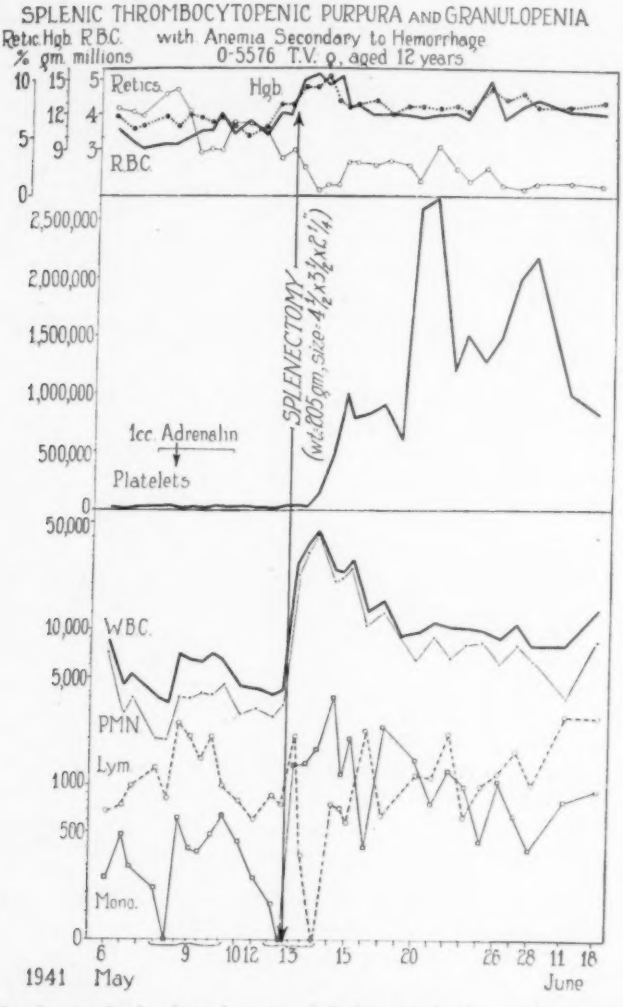

CHART 5. The hematologic data in case 4 before and after splenectomy. This case illustrates a type of hypersplenism in which the chief effect is exerted upon the platelets, whereas the neutrophilic leukocytes are depressed only moderately. The correction of levels of platelets and granulocytes was prompt and permanent. Note particularly the temporarily extremely high levels of both of these elements shortly following splenectomy. The charting of the white blood cells is upon a semi-logarithmic scale.

ecchymotic areas over right arm and shoulder and in right and left antecubital fossae. The gums were red, retracted, and oozing blood at several points; tonsils were hypertrophic but not grossly infected, with moderately enlarged, discrete, non-tender cervical nodes bilaterally and in the left axilla; the spleen was readily palpable on deep inspiration at the left costal margin; there was no hepatomegaly. Laboratory

data: total white blood cells 3400 to 5100, despite recent hemorrhages; total red blood cells 3,000,000 to 3,250,000; hematocrit 33 per cent; hemoglobin 11 gm. per 100 c.c.; reticulocytes 6.8 to 9.2 per cent; *blood platelets 6400 to 32,000 per cu. mm.* (normal 700,000); corrected erythrocyte sedimentation rate 0.3 mm. per minute (normal); erythrocyte fragility range .412 to .300; icterus index 5; prothrombin 60 per cent; representative supravital differential count of the white blood cells showed polymorphonuclear neutrophiles 56 per cent, eosinophiles 4 per cent, lymphocytes 34 per cent, monocytes 6 per cent, without significant qualitative abnormalities; bleeding time was 6½ minutes, Howell's coagulation time 10 minutes with delayed clot retraction. Hippuric acid excreted was 3.7 gm., urinalysis was essentially physiologic; serological tests for syphilis were negative. The sternal bone marrow on May 8 was grossly hyperplastic with red rather than gray tissue flecks; microscopically by actual count the RBC: WBC ratio was 5.1; normoblasts predominated with frequent mitotic figures observed in the few erythroblasts and occasional megaloblasts present; the myeloid elements were largely neutrophilic and at the myelocyte C or relatively mature stage with a few eosinophiles; the megakaryocytes appeared to be increased both relatively and in absolute number, as many as three being found in one oil immersion field, and were seen in every stage of immaturity from young, large mononuclear megakaryocytoblasts through intermediate to large, typical, mature granular megakaryocytes; only one plasma cell, an extremely rare phagocytic macrophage, and no monocytes or other cells foreign to normal bone marrow were encountered. The interpretation was, generalized pan-marrow hyperplasia of all normal cell types, with a significant left shift only in megakaryocytes, without evidence of toxic destruction or maturational arrest, therefore, a reflection of excessive peripheral demands for all types of circulating elements. The adrenalin test on May 9 showed a maximum rise in total white blood cells from the base line of 3450 to 7100 at the end of 15 and 50 minutes; red blood cells rose from 3,250,000 to 4,100,000 at the end of 50 minutes, and hemoglobin 11 gm. to 12 gm.; the platelets fluctuated between 32,500 and 14,000, the lower figures being recorded during the test.

Both the granulopenic leukopenia and splenomegaly, proved by direct and indirect evidence, are incompatible with a simple diagnosis of essential thrombocytopenic purpura. In no other instance of uncomplicated splenic purpura in our experience to date has the spleen been clinically palpable or at operation been found to be enlarged. The evidence seemed to justify the pre-operative diagnosis of thrombocytopenic purpura *and* granulocytopenic leukopenia, both attributable to splenic hypersequestration with compensatory marrow hyperplasia which also included the red cells a reaction secondary to the purpuric hemorrhages. Following parenteral administration of vitamin K and a blood transfusion of 200 c.c. to secure hemostasis, splenectomy was successfully accomplished on May 13 by Dr. Curtis. The temperature rose no higher postoperatively than the pre-operative base line between 100 and 101° F., and became normal for the first time in four months on the fifth post-operative day. On the day of operation the total white cell count rose from 3900 with 74 per cent polymorphonuclear neutrophiles at 9:00 a.m. to *44,400* with *96* per cent polymorphonuclear neutrophiles by 3:45 p.m., the spleen having been removed about 11:00 a.m. The red blood cells increased from 4,090,000 to 5,200,000, and the blood platelets from 16,400 to 165,580. This astounding increase in circulating granulocytes immediately following operation, in the absence of any infection or complication, reflects the tremendous compensatory hyperplasia of myelocytes in the bone marrow and the less stable hemolytopoietic equilibrium which we always find in children. The increase of approximately one million red blood cells per cu. mm. represents the reservoir sequestration of these elements in the enlarged spleen. The following day the platelets were 509,000 per cu. mm. and by the seventh post-operative day had risen to 2,616,000 per cu. mm. under the released productive capacity of the megakaryocytes. Under adrenalin

stimulation after exposure, the spleen contracted to approximately one-third of its gross size as first observed before the pedicle was clamped, and when removed, measured 4½ by 3½ by 2¼ inches and weighed 205 grams. Immediate supravital studies of the splenic parenchyma revealed a most striking abnormal segregation of polymorphonuclear neutrophiles, an occasional myelocyte C and eosinophilic granulocyte, and from one to three very large, highly phagocytic macrophages per oil immersion field containing many myeloid elements, fewer red blood cells, and much smaller material which could be interpreted as platelet debris. There was the usual number of qualitatively normal lymphocytes, and no increased fibrosis and no other pathologic cells or tissue changes were apparent. The patient was discharged on the fourteenth post-operative day in normal hematopoietic and clinical equilibrium, and when last seen June 18, 1941 she had 13,600 white blood cells, 4,270,000 red blood cells, hematocrit of 41 per cent, 13 gm. of hemoglobin, 832,000 blood platelets, 65 per cent polymorphonuclear neutrophiles, 7 per cent eosinophiles, 21 per cent lymphocytes, and 7 per cent monocytes.

Case 5. C. G., male, aged 34 years; final diagnosis: *subacute* splenic neutropenia, with thrombocytopenia and hemolytic anemia. This patient was well until May 5, 1938 when he developed a cough, sore throat, fever, and complained of easy exhaustion. A diagnosis of influenza was made by his physician. He did not improve, and the first record of a blood examination was made one month later at which time he was said to have an anemia. He was placed on liver and iron therapy but without improvement. A sternal marrow aspiration done at this time was reported as normal. Within the space of two months he received 11 blood transfusions. On December 19, 1938 an enlarged spleen was discovered and deep roentgen-ray therapy was given. During the succeeding nine weeks of his hospitalization he received two additional transfusions and two therapeutic injections of typhoid vaccine. In the meantime there had been four bone marrow studies, the last one of which was interpreted as "aplastic." Liver and iron were continued without improvement. Bleeding of the gums developed about one month prior to admission to the University Hospital. The past history included symptomatic and radiological evidence of peptic ulcer of 12 years' duration. The patient was a glazier by occupation but had had no contact with lead.

Upon admission to the University Hospital research service (B. K. W.) the physical examination showed a well nourished but apprehensive male patient of the stated age with an icteric pallor to the skin, sclerae, and mucous membranes. Minimal but generalized adenopathy was present with an enlarged spleen extending two cm. below the left costal border. No other significant physical abnormalities were noted. The laboratory data included: peripheral neutropenic leukopenia, moderate anemia and marked thrombocytopenia (chart 6). The bone marrow differentials revealed panhyperplasia for all elements but more particularly the nucleated red cells. Urinalysis was normal. The basal metabolic rate was minus 21 per cent; checked at minus 22 per cent. The Wassermann and Kahn reactions were negative. The hippuric acid excretion was 4.5 gm. in two hours. The blood chemistry revealed a fasting blood sugar of 112 mg. per cent, blood urea nitrogen of 15 mg. per cent, total proteins of 7.5 per cent. The electrocardiogram showed a slight left axis deviation, and the chest roentgen-ray was negative for any pathologic process. The temperature and pulse were within physiologic limits. Splenectomy was performed on May 12, 1939 by Dr. V. A. Dodd, of the Department of Surgery. The presence of a duodenal ulcer was confirmed, but all other abdominal viscera appeared normal except the enlarged spleen about which numerous friable adhesions were found, possibly the result of the previous roentgen-ray therapy. During the manipulation of the spleen incident to its removal, a 50 per cent shrinkage occurred. An immediate granulocytosis followed, with a typical somewhat delayed thrombocytosis, such as we have described in essential thrombocytopenic purpura.[4] The rise in red blood cells dupli-

cated that seen in congenital hemolytic icterus following splenectomy.[5] The postoperative convalescence was complicated by temporary atelectasis of the left lung, followed by a mild bronchopneumonia, non-specific in type, which resolved satisfactorily, the patient being discharged on June 14, 1939. When seen two months after operation, the patient had no symptomatic complaints, and all the cellular elements were normal qualitatively and quantitatively in both blood and bone marrow. This recovery has been maintained up to and including the present writing (2½ years).

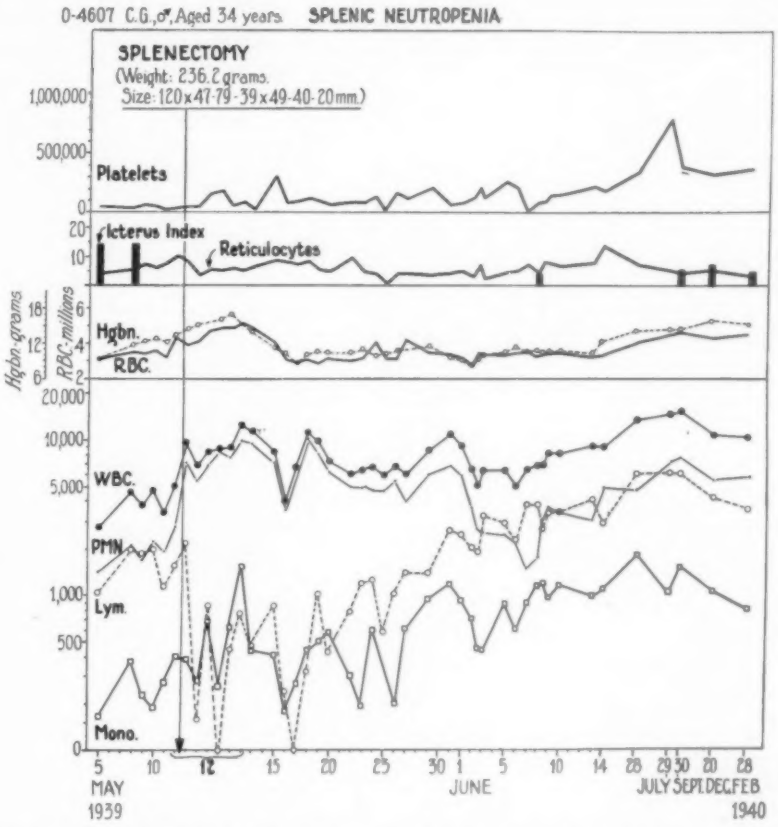

CHART 6. The hematologic findings in case 5 before and after splenectomy. Prior to operation this patient presented a depression chiefly of the platelets and granulocytes. The increase of the platelets to normal levels following splenectomy was relatively slow, that of the neutrophilic leukocytes was immediate. The charting of the white blood cells is upon a semi-logarithmic scale.

DISCUSSION

An analysis of the preceding cases shows the "common denominator" of all to have been profound granulopenia, panhyperplasia of the marrow and splenomegaly, with splenectomy curative. Varying degrees and combinations of hemolytic anemia and thrombocytopenic purpura were encountered and coincidentally corrected. In each case the anemia was hemolytic in type, with elevated reticulocyte count and icterus with negative direct van den

Bergh reaction. Case 1 showed principally neutropenia but also definite thrombocytopenia and hemolytic anemia. Case 2 although exhibiting chiefly neutropenia when first seen, had developed two months later not only a more profound neutropenia, but also a hemolytic anemia and thrombocytopenia of rather severe grade. Case 3 showed the most extreme and pure example of neutropenic leukopenia, at no time evidencing any hemolytic anemia, but developing some non-symptomatic thrombocytopenia by the second admission. Case 4 is instructive from the standpoint of the thrombocytopenic purpura which was the most striking presenting feature upon hospitalization, but probably represented a secondary manifestation of primary splenomegalic neutropenia when all of the facts are weighed critically. Case 5 showed initial infection with subsequent neutropenia and icteric anemia, and finally bleeding gums (thrombocytopenia), all of which disappeared after splenectomy. From these facts there is little doubt that a single mechanism is responsible for the various degrees of anemia, neutropenia or thrombocytopenia in this group of cases, especially when it has been demonstrated that all three elements are increased following splenectomy. In addition, it has been shown through direct supravital studies of the splenic parenchyma that there is a marked increase in number and phagocytic activity of the macrophages, each one of which is seen to be actively destroying not only neutrophilic leukocytes (and in some instances myelocytes) but also red blood cells, including normoblasts to a lesser degree. One can only conclude that the syndrome is directly a result of hypersplenism, in which there is not only an accentuation of the physiologic function of disposing of effete, senile or damaged circulating blood elements, but also the development of a pathologic predilection for young, nucleated, as well as normal mature cells. We visualize this syndrome, therefore, as closely akin to congenital hemolytic icterus and essential thrombocytopenic purpura and possessing a comparable mechanism. In the former disease, the activation of the clasmatocytes of the spleen is directed chiefly toward the red blood cells, in the latter chiefly toward the thrombocytes, and in the neutropenic syndrome chiefly toward the neutrophilic leukocytes. A review of our cases of congenital hemolytic icterus and thrombocytopenic purpura reveals that each is often accompanied by a more or less definite reduction in other circulating units, including the white cells.

It is not felt that the syndrome discussed in this paper is to be confused with Banti's syndrome since in no instance has there been any functional or direct evidence of portal hypertension or cirrhosis of the liver. Furthermore, Banti's syndrome is always characterized by recurring anemia secondary to esophageal or gastric hemorrhages, never by a hemolytic type of anemia, the latter being quite definite in several of our cases. And in the patients described here, purpura was occasionally observed, but seldom if ever massive hemorrhages, and none of the spleens removed at operation in our syndrome of leukopenia showed the histopathologic features described for Banti's syndrome.

The limited data available in Felty's [6] reported cases do not permit either of their inclusion or exclusion in the syndrome described. Two of our patients had a history of joint pains, but this symptom was negligible during the acute neutropenic episodes. Felty's original five cases each showed a moderate leukopenia but in no instance so severe a neutropenia as in our series. Although a slight secondary anemia was recorded, jaundice was not mentioned nor other evidence given upon which to postulate an underlying hemolytic mechanism. Hanrahan's case [7] of Felty's syndrome, except for the arthritis which was a prominent feature, more closely parallels the present series in that there was an appreciable anemia and thrombocytopenia, and it is stated that "larger cells exhibiting red blood cell phagocytosis were plentiful in the sinuses" of the spleen. Restitution of both red and white blood cells to normal was found months after splenectomy. As has many times been pointed out and as our own experience has verified, atrophic arthritis is often associated with some anemia and a moderate leukopenia, and in the young individual there is often splenomegaly (Still's disease). As Felty himself pointed out, his syndrome may represent Banti's disease with coincidental arthritis, although he believed he was dealing with a different clinical entity. Williams [8] in reporting a case of so-called Felty's syndrome, suggests that it may represent a primary disturbance of blood formation in which there is an arrest of maturation of the granulocytes. Postmortem studies showed a diminution in granulopoiesis in the bone marrow, the direct opposite of the findings in all of our cases. Cravens' case [9] resembles our syndrome only remotely. Price and Schoenfeld's case [10] with postmortem studies showed only a very slight neutropenia. There was a minor degree of myeloid hyperplasia in the bone marrow but no change in the spleen such as we have described. Without sufficient data in each individual case precisely to define its limits and, therefore, its mechanism of production, these overlapping syndromes must remain symptomatically closely related but probably etiologically distinct. The therapeutic approach to each clinical problem must depend upon the accurate determination of its fundamental, underlying cause.

Furthermore, we do not believe that we are describing a syndrome that is fundamentally an infectious process, although, like congenital hemolytic icterus and probably essential thrombocytopenic purpura, the clinical and hematologic features may become apparent or the syndrome be precipitated during or following an infection. The association of splenomegaly and leukopenia with a wide variety of chronic infections is too well known to require extended comment; however, the combination of thrombocytopenia, severe neutropenia with myeloid hyperplasia in the bone marrow and hemolytic anemia are not the classical features of chronic infections.

Malignant neutropenia, drug induced or otherwise, is readily differentiated by a good history, clinically by absence of an enlarged spleen and hematologically by the bone marrow which is hypoplastic for myeloid elements with marked maturation arrest.[11]

Leukemia of sub-leukemic myeloid type may present the most difficult differential diagnosis. Here a critical examination of bone marrow supplementing carefully made blood studies is all important in that splenic neutropenia never shows the qualitative alterations in the myeloid elements which characterize the myeloid leukemias.

TABLE IV

Splenic Neutropenia

Diagnosis

I. Clinical:
   1. Splenomegaly
   2. Occasionally purpura (depends on degree of associated thrombocytopenia)
   3. Occasionally oral ulceration (depends on acuteness and severity of neutropenia)
   4. Occasionally mild icterus (depends on degree of associated anemia)

II. Hematology
   1. Bone marrow
      a. Hyperplastic for myeloid series and, if hemolytic anemia is pronounced, erythroid series.
      b. No abnormal cells present
      c. Not leukemic
   2. Blood
      a. Marked specific neutropenia
      b. Anemia when present is macrocytic, hyperchromic in type
      c. Reticulocytosis if anemia is definite
      d. Increased indirect van den Bergh depending on grade of anemia
      e. Thrombocytopenia variable

A summary of the essential diagnostic criteria is given in table 4. In general, from a clinical standpoint we feel that the presence of an easily palpable non-tender spleen is the most important feature. If, then, a severe neutropenic leukopenia with variable even though slight anemia and thrombocytopenia is found and if the bone marrow shows panhyperplasia including the myeloid elements without maturation arrest or pathological alterations, the diagnosis should be sufficiently certain to justify the therapeutic test of splenectomy.

We feel that the completeness of the recovery and the time interval that four of these patients have survived since our preliminary report [1] without any signs of relapse definitely eliminates any other diagnosis or mechanism such as hypoplastic anemia or subleukemic leukemia.

CONCLUSIONS

1. A newly recognized syndrome characterized by marked neutropenia and splenomegaly has been described. It is suggested that this be termed essential or primary splenic neutropenia, inasmuch as evidence is adduced to show that the basic mechanism is hypersplenism in which an accelerated destruction of the granular leukocytes of the circulating blood by the reticuloendothelial cells of the spleen takes place.

2. The disease is apparently permanently cured by removal of all splenic tissue, and the patients are restored to normal hemolytopoietic equilibrium.

3. Although this syndrome may superficially resemble Banti's syndrome, Felty's syndrome, sub-leukemic myeloid leukemia, hypoplastic anemia, ma-

lignant neutropenia, or certain types of chronic infection in one or more particulars, it nevertheless is a separate and distinct entity based solely upon splenic dysfunction. In this respect primary splenic neutropenia is more closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, each of these predominant clinical and hematologic syndromes blending into and involving to a greater or lesser degree the other. The reticuloendothelial cells of the spleen when on a rampage of destruction, may selectively choose as victim any *one* of the elements of marrow origin passing through this organ, but more often than not other "innocent bystanding" elements suffer likewise in some degree. Splenectomy always is followed by an increase in *all* circulating blood elements whenever applied in any one of these conditions.

4. An accurate final diagnosis may be achieved only after complete clinical information plus detailed studies of both the blood and bone marrow.

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NON-OPERATIVE RESULTS IN NINETY PATIENTS WITH ABNORMAL CHOLECYSTOGRAMS *

By Staige D. Blackford, M.D., F.A.C.P., Robert M. Bird, Jr., M.D., and S. Ward Casscells, M.D., *University, Virginia*

The literature contains many reports indicating the effectiveness of medical treatment in gall-bladder disease. However, Walters and Snell [1] believe that in many of these reports there is an element of wishful thinking in the interpretations of the results. They point out that long-term observations of large groups of medically treated patients are rare, and they cite the report of J. M. Blackford, King and Sherwood [2] as one of the best. In that report, 200 cases diagnosed clinically as cholecystitis were reviewed by follow-up methods after an average period of nine and one-half years. However, the large majority of these cases were studied before cholecystograms came into use, and hence no attempt could be made to correlate the non-operative results with the cholecystographic examinations. It is the purpose of the present study to analyze the non-operative results obtained in a routine group of 90 patients with abnormal cholecystograms.

Selection of Cases. Records of more than 500 abnormal cholecystograms were found in the files of the Department of Roentgenology of the University of Virginia Hospital from 1925 to 1938. Wilson, Lehman and Goodwin [3] reported the results of surgery in 252 of these cases which came to operation. One hundred and eighty-five of the remaining cases had records available which were suitable for this study.

Follow-up Method. A printed questionnaire was mailed to each of these 185 patients and, in most instances, to their local physicians. The questions in the form related to the following: (1) Subsequent indigestion; (2) food idiosyncrasies; (3) occurrence of abdominal pain; (4) occurrence of colic; (5) occurrence of jaundice; (6) treatment followed; (7) subsequent operation; (8) ability to lead a normal life; and (9) patient's own estimate of any change in the status of symptoms after the cholecystogram.

Satisfactory replies were received from 90 of the 185 patients (43.7 per cent). The average period of follow-up in these cases was six and one-half years.

Initial Clinical Data

General. The average age was 50.3 years. There were 57 females and 23 males. Five were colored.

Symptoms. The symptoms of these 90 patients were graded from their records at the time of the initial cholecystogram as mild, moderate and severe. In the mild group of 25 patients, there were many who had no symptoms

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From the Department of Internal Medicine, University of Virginia Hospital.

referable to the gall-bladder and in whom the cholecystogram was performed merely as a part of a general diagnostic survey. The others in this group were those who suffered with mild dyspepsia. There were 26 patients whose symptoms were classified as moderate, meaning that their general health was fair but that they suffered from bothersome indigestion, right upper quadrant pain, nausea or vomiting, either singly or in combination. None of these cases had either colic or jaundice. The severe group was comprised of the 37 patients who complained of severe right upper quadrant pain, colic, jaundice or frequent severe indigestion, singly or in combination. The patients in this group would probably have been diagnosed clinically as having cholecystitis. The records in two remaining cases were inadequate to grade the severity of symptoms.

Cholecystograms. Of the 69 patients without demonstrable stones, 29 had non-functioning gall-bladders at the time of the original roentgen examination, and 40 patients had poor function. Of the 21 cases with stones, six had non-functioning gall-bladders, nine poor function, and six good function.

Reasons for No Operation. In 33 patients, it was felt that the gall-bladder symptoms were too mild to justify surgical interference. A trial on medical treatment before recourse to surgery was thought advisable in nine instances. Operation was recommended to 23 patients but they refused surgery. The operative risk was considered too great in 17 patients. No cause for delay in surgical treatment could be assigned from the records in eight cases.

Treatment

Medical. The exact medical treatment advised in 57 cases is known from the records. It seems reasonable to assume that some similar advice was given to a majority of the remaining patients. Although the medical treatments instituted followed no set routine, in general the following points were stressed: (1) a bland diet suited to the individual's caloric needs and dietary idiosyncrasies; (2) fat content of the diet adjusted to the individual's tolerance; (3) antispasmodic drugs when indicated; (4) choleretic drugs occasionally; and (5) sedatives if necessary. Many patients were placed on a simple bland diet with frequent feedings. It is impossible to say how closely the instructions were followed and what other remedies were used. Numerous patients attributed their improvement to various patent medicines which they had begun on their own initiative.

Surgical. Ten of the 90 patients are known to have come to subsequent cholecystectomy. Three of these had non-functioning gall-bladders, five had poor function, and two had stones.

Non-Operative Results

Deaths. Fifteen of the 90 patients, on whom questionnaires were returned by their families, are dead. Two of these are said to have succumbed

to "gall-bladder attacks"; neither was subjected to surgery because of their advanced years. Two other fatal cases were jaundiced at the time of the cholecystogram. One of these died in the hospital without diagnosis while awaiting laparotomy. The other died on re-admission for alcoholic hallucinations, apparently from acute hepatitis. In 11 of the 15 fatal cases, death was attributed to causes outside the hepatic and biliary tracts.

Method of Grading the Non-Operative Results. The symptomatic results in the 90 patients were graded in a manner similar to that employed by Wilson, Lehman and Goodwin [3]:

Grade 1: Excellent results. Good general health without recurrence of symptoms; no food idiosyncrasies; patient able to do ordinary work.

Grade 2: Good results. Good general health with only mild digestive disturbances or occasional upper abdominal fullness; few foods not tolerated; no work loss.

Grade 3: Fair results. Fair health with bothersome digestive upsets with or without right upper quadrant pain; work loss.

Grade 4: Poor results. Poor health; colic or frequent abdominal pain. The patient in this group considers himself the same or worse than before roentgen study.

Patients falling into groups one and two have been termed "satisfactory" and those in groups three and four "unsatisfactory." All cases which came to subsequent operation have been grouped under "unsatisfactory" even though three of these 10 were no better following surgery.

After the 90 questionnaires were graded as satisfactory and unsatisfactory, the results were correlated with: (1) severity of the original symptoms; (2) reason for delayed operation; and (3) initial roentgen report.

1. *Non-Operative Results Correlated with Severity of Original Symptoms.* The results were graded as satisfactory in 68 per cent of those whose original symptoms were classed as mild, in 50 per cent of those classed as moderate, and in 35 per cent of those classed as severe.

2. Non-Operative Results Correlated with Reason for No Operation.

Reason	No. of Cases	Total Deaths	Symptomatic Results	
			"Satisfactory"	"Unsatisfactory"
Advised but refused	23	4	7	16
Preliminary medical treatment advised	9	0	2	7
Too few gall-bladder symptoms	33	4	23	10
Too poor operative risks	17	5	7	10
Unknown	8	2	4	4
Totals	90	15	43	47

3. *Non-Operative Results Correlated with Initial Roentgen Report.*

Roentgen-Ray Report	No. of Cases	Total Deaths	Subsequent G. B. oper.	Symptomatic Results	
				"Satisfactory"	"Unsatisfactory"
Poor function.....	40	3	5	21	19
Non-function.....	29	10	3	13	16
Stones					
N.F.....	6	2	1	4	2
P.F.....	9	1	0	3	6
G.F.....	6	0	1	2	4
Totals.....	90	15	10	43	47

It will be seen from the above that the symptomatic results were graded as satisfactory in 47.7 per cent of the entire 90 patients with abnormal cholecystograms, in 52.5 per cent of those with poor function, in 44.9 per cent of those with no function, and in 42.8 per cent of those with cholelithiasis.

Comment

The pitfalls of this study are apparent. Aside from the fallacies inherent in all questionnaire follow-ups, the total number of cases is too small for any statistical conclusions. Furthermore, in any attempt at analysis, the total would have to be broken down into even smaller groups on account of the variability in symptomatology and cholecystographic data. However, it seems justifiable to present this material in the hope that it may be amplified by other reports of a similar nature.

It should be pointed out that the results presented here are called non-surgical rather than medical results. It was obvious from the replies that relatively few of these patients followed faithfully the medical régime advised. But even in those who adhered strictly to the instructions given, there was no appreciable favorable difference in the results obtained. It is difficult to see how medical treatment of gall-bladder disease can affect its course other than by relief of symptoms which for the most part are not directly attributable to the gall-bladder itself. It is believed that the results here reported represent to a large extent the natural course of the condition rather than specific results of medical treatment. It should be noted that medical treatment was considered the treatment of choice in only 10 per cent of the present group.

From the symptomatic point of view, many of these patients with abnormal cholecystograms did not have sufficient symptoms to warrant a clinical diagnosis of cholecystitis. However, cholecystitis would presumably have been the clinical diagnosis in the 37 patients whose symptoms were classified as severe. It is interesting that symptomatic relief was graded as "satisfactory" in 35 per cent of this group as compared to 37 per cent in the group clinically diagnosed as cholecystitis reported by J. M. Blackford and associates.[2]

When the present results are compared by the same criteria with those recorded by Wilson, Lehman and Goodwin [3] from the same institution, it is found that "satisfactory clinical results" are obtained in 79 per cent of cases of cholelithiasis by surgery as opposed to 43 per cent without surgery. This appears to favor surgery for cases of cholelithiasis with symptoms. On the other hand, in those with abnormal function alone on cholecystogram, the 64 per cent relief from surgery does not contrast so favorably with the 49 per cent relief without surgery. And finally, the 3.6 per cent operative mortality is about as large as the mortality from biliary causes over six and a half years in the present series.

It is not our purpose to discredit surgical treatment of gall-bladder disease, but we wish to point out that this small series of cases would again indicate: "the patient with uncomplicated cholecystitis should be given a trial on medical treatment and if not promptly relieved, he should be operated on." [2] Watchful waiting may obviate a major surgical procedure, and it appears to be about as safe.

Summary

Ninety patients with abnormal cholecystograms were not subjected to immediate surgery. Over six and one-half years' average follow-up, the non-operative results were "satisfactory" in 47.7 per cent of the group. Satisfactory results were found in 52.5 per cent of those with poorly functioning cholecystograms, in 44.9 per cent in those with non-functioning cholecystograms and in 42.8 per cent of those with cholelithiasis.

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HEART STRAIN: A CRITICAL REVIEW; THE DEVELOPMENT OF A PHYSIOLOGIC CONCEPT *

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Many of the obstacles in the path of modern cardiologic progress have been swept aside in the past 50 years, and the cardiologist of today can negotiate the highways and byways of his specialty with comparative ease. His chief concern at present, therefore, is to keep these hard won pathways of knowledge clear and, from time to time, add his bit to the sum total of amassed information.

One field, however, still remains unexplored, that of heart strain. The subject is not a new one but is certainly an unsettled and misunderstood one. The law courts, insurance companies, compensation boards, industrial and military physicians, and last but not least, the cardiologists will readily attest to the consternation, conflict of opinion, involved logic, and general dissatisfaction a case of so-called "heart strain" can produce. Since this is such an important phase of cardiology and, at the same time, such a controversial one, we feel that an airing of the entire subject is long overdue.

We are presenting this work, therefore, bringing to the attention of the medical profession the accumulated evidence on both sides of the subject, with the fervent hope that by stimulating a renewed interest, all of us may be helped to a final solution of a problem which still remains unsolved.

The first source of confusion in dealing with the question of heart strain has been the lack of a comprehensive yet concise definition of the subject. The earlier writers seemed to have felt that there was no need for such a specific delineation, leaving one with the inevitable impression that heart strain differed in no way from strain of one or more of the somatic muscles. In order, then, to have a foundation for discussion, we shall define heart strain as: *That condition which produces myocardial damage, secondary to some unusual effort.* As we consider this definition, it becomes immediately apparent that this could not be applied to those cases of so-called heart strain which are supposedly due to prolonged, hard labor over many years and which the older writers, such as Allbutt, considered as the etiologic factor.[1] This then brings us to the first point that must be cleared up. Heart strain must be divided into two types, those which are produced by some sudden effort or strain, and those resulting from effort spread over a long period of time. The first we shall call "acute heart strain," and the second we shall designate "chronic heart strain." We will now consider the evi-

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dence for each type separately, since this has been, we feel, the basis for much of the confusion which has arisen.

Acute Heart Strain. The definition stated above seems to be most adequate for this portion of the subject, and with this in mind let us examine first the syndrome which has been covered by it before we attempt to gather evidence to prove or disprove it. The etiology of this condition, as presented by Kahn,[2, 3] follows:

a. *Occupations*—those causing sudden severe stress to be placed upon the heart, though these may ordinarily be light in character.
b. *Chronic infections and intoxications*—these may act upon the myocardium and so act as an important contributory factor, though this cannot be proved.
c. *Previously existing heart disease*—the acute strain may aggravate this condition.
d. *Age*—this is important in that after the age of 40 there is a substitution of fibrous instead of elastic tissue, especially in the aorta, with consequent lessened elasticity and subsequently less resistance to strain.
e. *Sex*—more common in males only because they are more often engaged in industry, though there are cases recorded in females.
f. *The exciting cause of heart strain*—excessive exertion such as lifting, pulling, pushing, straining, stair or mountain climbing, especially while supporting a load,[2] coughing or laughing.[4]
g. *Nervous strain, fatigue or excitement*—these may also cause heart lesions, but to what degree remains problematic.[5]

To summarize, therefore, we can say that acute heart strain occurs in the healthy or diseased heart, either in the male or female, when there is an unexpected sudden severe stress placed upon the heart due to some unanticipated, added physical strain thrown upon a person who is already doing almost capacity work.

The symptoms of acute heart strain are considered to be as follows[3]:

a. *Onset:* To be considered, the symptoms must come on during or immediately after the performance of some strenuous work, when cardiac stress and aortic pressure are at a maximum.
b. *Pain:* This may vary greatly and still be significant. It may be precordial or substernal in location.
c. *Weakness:* This varies from just a disabling weakness to complete unconsciousness.
d. *Dyspnea and palpitation:* These two symptoms occur at the time of onset of the condition and often become permanent, growing worse with time or effort.
e. *Disability:* The cardiac response is definitely limited after an acute strain, with any exertion producing marked cardiac symptomatology.

f. Heart failure: If the patient continues to work, the symptoms of heart failure often ensue.

g. Death from primary heart strain: This occurs as a rule only when some preëxisting cardiac pathologic lesion is aggravated by the strain.

Almost the same set of symptoms for acute heart strain is listed by Peacock, emphasizing the fact that when this condition is seen, it is fairly characteristic within certain wide limits.[6]

The physical findings in the typical case are extremely variable, as is to be expected. These vary from simple tachycardia to complete collapse[3]:

a. Rapid pulse rate, usually with a small pulse.[1]

b. Auricular fibrillation often occurs at once with frequent recurrences.[4]

c. Irritable heart with its attendant symptoms may be found.[7]

d. Murmurs at one or another of the valve areas which may be due either to rupture of the valve, or to functional changes after the severe strain.[5, 6]

e. Cardiac dilatation may be found at times.[2]

f. Tender spots may be found on the chest wall over the precordium.[3]

g. Various arrhythmias other than fibrillation may also be found after an acute strain, such as extrasystoles, flutter and paroxysmal tachycardias.[5]

h. The electrocardiogram may show various changes in the T-waves, such as inversion in various leads, and at times even bundle branch block is seen.[3, 5]

In the course of time there will, of course, occur certain changes which will depend largely upon the seriousness of the original damage. When heart failure supervenes its set of symptoms must be added to the others.

Having outlined these criteria of acute heart strain as a basis for discussion let us examine the literature both for and against such a concept. Allbutt was impressed by the fact that in a large laboring population many of the young, healthy males had heart ailments, and upon close observation he became convinced that strain of effort was the common factor at the root of these cardiac difficulties. He felt that overstretching of the heart muscle fibers beyond their physiologic limits could cause alterations of the molecular structure of the fibers, thereby producing a permanent damage that would be progressive in character.[1] Bainbridge, although he admits the difficulty of scientific proof, agrees with this theory. However, he does straddle the fence somewhat, since he limits such strain to middle life or to postinfectious states when there has already been some impairment of the myocardial circulation.[8] Eyster, from his experimental work in increasing the load on the heart of dogs by placing constricting bands about their aortas for varying lengths of time, concludes that cardiac hypertrophy that develops in organic heart disease is not owing to the increased work of the muscle per se, but to the muscle injury and the reaction to the injury that result

from the abnormal stretching of the muscle in the initial period of the overload. He states further that the overload upon the heart need last but a very short time in order to produce muscle injury which will later allow hypertrophy and failure to develop. In spite of these findings in his work upon animals, Eyster does not feel that the same condition can occur in man unless there has been some cardiovascular disease already present prior to the load being placed upon the heart.[9] This statement further emphasizes the state of confusion in which we find ourselves whenever heart strain is the subject of discussion. Although all the experimental work seems to point toward the existence of such an entity, Eyster denies this because of his normal heart findings in a group of athletes. The experimental work showing that heart muscle injury does occur after an undue load has been placed upon the heart, with resultant heart failure subsequently, is certainly convincing enough. The question of the athlete's heart will be discussed in a later chapter.

Clinically, on the other hand, many observers felt that acute heart strain can and does occur. Peacock, in 1865, presented several cases to prove his contention that cardiac strain resulted when sudden stress was thrown upon the heart.[6] Allbutt proposed much the same concept.[1] DaCosta, in his now historical article on the irritable heart, speaks of heart strain as a true entity.[7] Kaufmann, in his equally careful studies, found that cardiac enlargement can and does occur after exertion.[10] Hay and Jones were particularly interested in the development of auricular fibrillation as a result of heart strain and quote several cases to illustrate their point.[4] The Kahns, in their several papers on this subject, have, of course, presented a very complete brief for the concept of heart strain.[2, 3, 11] They have painstakingly reviewed the literature and present most convincingly arguments in defense of their conclusions and cite many cases of their own as well as those of others to substantiate their rather positive and at times dogmatic views. Christian says that strain may cause subsequent cardiac hypertrophy and then dilatation.[12] White and Glendy, in their chapter on "Trauma and Heart Disease," in Brahdy and Kahn's recent book, state that their review of the literature also makes them feel that heart strain is one of the forms of trauma which is capable of producing cardiac damage.[5]

This presents but a short summary of the opinions of those men who have contributed the most outstanding papers upon the affirmative side of the question as to whether there is a clinical entity which can be designated as heart strain and which, in turn, is capable of producing cardiac damage of a nature severe enough to result in a fatal termination in many instances.

There is, of course, an equally emphatic group which is entirely opposed to the above concept. Gordon and Strong exercised normal rabbits and those whose hearts had been enlarged by the use of adrenalin and spartein sulfate, until the animals were exhausted, and found a contraction of their heart size, in the exhausted state, of about 19 per cent. (The weight silhouette method was used to determine heart size before and after exercise.)

The animals all recovered within a short space of time and seemed to have suffered no ill effects at the end of a two-month observation period. Gordon and Strong conclude, therefore, that exercise causes the heart to get smaller and so there could be no heart strain.[13] This question of exercise and its effect upon heart size will be discussed later and the fallacy of the above argument shown.

Barron says that the normal heart does not increase in size, no matter how great the load that is placed upon it. However, he goes on to say that when the myocardium has been weakened by disease, then a load may be placed upon it which will exceed the physiologic limit of the muscle, producing a dilatation. This in turn causes weaker muscular contractions, with lessened efficiency and subsequent further dilatation and finally failure.[14]

Sir Thomas Lewis has been the greatest opponent of the theory of heart strain. He feels that the heart cannot dilate beyond physiologic limits because of the fibrous pericardium. He summarizes his views by stating "if strain of the healthy heart exists, it is no more than a curiosity." [15] In some of his later work he does, however, feel that valve cusps may rupture during violent body effort with resultant dilatation of the heart. Yet even here he presupposes that the heart was not healthy to start with.[16]

This, in substance, is the evidence for and against the concept of acute heart strain. We can readily see that the question resolves itself into the weight of authority as represented by Sir Thomas Lewis on the one side, as against the weight of clinical evidence in favor of the entity. Lewis places all his emphasis upon the fact that the heart muscle can withstand any strain so long as it is not already diseased. It is pertinent to point out here that all the workers in favor of the concept have kept this precept in mind and have carefully checked each of their cases to rule out such a possibility, yet they still felt that they found cases of heart strain clinically. Therefore, on the basis of the work of these clinical investigators, coupled with our own experience, we conclude that acute heart strain is a distinct and well-defined clinical syndrome. In this connection, let us see whether we can refute Lewis's arguments against the concept so that we will also be able to strengthen our cause on a theoretical basis as well.

The animal work of Eyster, which was previously quoted, showed very conclusively that a load thrown upon the healthy heart, even for a relatively short time, is capable of causing damage sufficient to produce subsequent failure. Though the strain thrown upon the hearts of these animals was not quite comparable to that seen in acute heart strain, there is enough similarity in that it proves very definitely that the healthy heart may be damaged by a sufficiently severe load.[9] This work pretty definitely shows that enough of a strain can be thrown upon heart muscle to damage the fibers so that hypertrophy and finally cardiac failure will ensue. In this way Lewis's chief argument becomes untenable.

Not only in animals may we demonstrate the fact that rupture of the cardiac muscle may occur; there are many references in the literature to

cases of rupture of the human heart muscle, of the valve cusps, the development of arrhythmias, as the result of mild blows upon the chest, or even indirectly from trauma localized in the abdomen or parts of the body other than the chest.[5, 11, 17, 18, 19, 20, 21, 22, 23] Autopsies on several of these patients show that the rupture occurred through a portion of the myocardium which appeared to be normal in every way except for the rent in it.[18, 19, 20] Bilderbeck, citing one of his cases, advanced the suggestion that the probable cause of the heart rupture was the sudden compression of a right auricle which became engorged due to the patient holding his breath in deep inspiration just before the blow struck.[19] The same view is presented by Glendy and White, who feel that an important factor in heart wall rupture is the distention of the heart chamber at the end of diastole or the beginning of systole; at this time any sudden or extreme pressure is far more apt to cause the heart to rupture whether it is diseased or not.[5] Lewis himself records the fact that when a deep inspiration is taken with the glottis closed the heart is seen to dilate very markedly and remain in this state as long as the inspiration is maintained, though it invariably will return to normal when the breath is released.[16]

With these facts in mind let us picture a man lifting a weight which is at about the limit of his capacity; his every muscle is strained, his neck veins are engorged, and in all likelihood he is holding his breath (the picture presented by Lewis). Suddenly this man slips, or the load teeters, or something else happens which demands an added sudden effort. May we not then conceive that with the heart already distended, the increase in pressure brought on by that sudden added effort adds the last straw, and there is a rupture of some of the muscle fibers, or else there may be a rupture of a small blood vessel with resultant myocardial damage. After such heart muscle has once been damaged, further changes may occur.

Harrison says that if increase in heart fiber size is due to increased load on that fiber, then increased work of the heart as a whole, or disease of other fibers would throw a greater burden on the sound fibers with resultant hypertrophy. Dilatation then results when the hypertrophy fails adequately to take care of the increased demands upon the heart.[24] Willius and Smith, and Thompson and White feel much the same way about the causes of hypertrophy and dilatation.[25, 26] So then, in the acute strain, after the fibers are damaged, if it is severe enough, there will be an added burden thrown upon the sound fibers with hypertrophy and then failure. This then is the probable explanation of why Eyster's dogs showed cardiac changes long after the load had been removed.[9]

Let us assume, however, for the sake of argument, that Lewis is right, and it is impossible to tear a heart muscle fiber. Could we still explain the occurrence of acute heart strain? The answer is yes. There is enough evidence in the literature to show that one may get a relative coronary insufficiency with ischemia and anoxemia of a portion of the myocardium. The man who is working at full capacity, and who then adds a little more to his

exertion, may suddenly find himself with an inadequate blood supply to a portion of his myocardium with resultant changes identical in every respect to those seen after a coronary occlusion or thrombosis. The sequence of events after such an occurrence can be just as varied as those seen after a true occlusion.[27]

There is some experimental work which shows pretty definitely that by distending the left ventricle one may produce arrhythmias of variable kinds, especially ventricular tachycardias.[28] Once a tachycardia is established it is simple to conceive of either a ventricular fibrillation occurring, or with a reduced cardiac output due to the shortened diastolic period, a relative coronary insufficiency ensuing. Since we know that there can be overdistention of the ventricle in heart strain, as previously pointed out, this series of events can also be anticipated.

We have, then, enough evidence to show that a man who is working at his limit of capacity, may, by a sudden added exertion, produce damage to his heart in one of several ways.

In summary, therefore, we may say that our definition of acute heart strain as "that condition which produces myocardial damage, secondary to some unusual effort," can be justified on the bases of both experimental and clinical work. Clinically, it is a condition in which substernal or precordial pains come on suddenly during an *unusual effort,* producing certain changes which can be determined objectively. If this concept is kept in mind, we shall have an entity which can thus be recognized.

Chronic Heart Strain. Having presented the picture of acute heart strain, we shall now carefully consider the other phase of the question, i.e., chronic heart strain. Though many have dealt with this concept since Allbutt first discussed it, no one seems to have crystallized the thought conveyed by the phrase.[1] We shall, therefore, define the idea as presented by the various authors who have been much interested in this topic. For the sake of argument, chronic heart strain may be defined as an *organic condition, associated with the sudden or gradual onset of symptoms referable to the cardiovascular system which can be attributed to severe muscular effort over a long period of time, resulting in physical disability of varying degree and duration.* It is self-evident that this definition leaves out a great deal that is important and is, therefore, open to severe criticism. However, this seems to be the only definition that will adequately cover the concept as most authors present it. Having defined the subject, we may now proceed to a consideration of the etiologic factors:

a. Occupations—any one which demands prolonged heavy exertion.[1, 3, 6]
b. Athletics—running, swimming, weightlifting, and rowing.[1, 22]
c. Age.[3]

In other words, any heart which is subjected to full capacity demands at frequent intervals, for long periods of time, either because of occupation or avocation, is likely to begin to fail owing to the chronic strain placed upon it.

The physical findings of cardiac failure are too well known to need repetition here.

The pathology here seems to be quite definite. The following are the most important findings [2]:

a. Atheroma of the aorta and arteriosclerosis.
b. Hypertrophy of the heart.
c. Cardiac dilatation.
d. Coronary artery disease.
e. Aneurysm of the left ventricle.
f. Aneurysm of the aorta.
g. Temporary diminution of tone or contractile power of the heart, as seen after fatigue.

Allbutt gives much the same picture of the pathology of this condition in his paper.[1]

At this time let us once more "examine the record" and decide whether we are dealing with an entity or not. The Kahns feel very definitely that chronic stress plays havoc with the myocardium and leads to failure.[3] Allbutt found many examples of heart disease in "young, well-made subjects of healthy build, and previously unaffected by constitutional disease." "After a time," he says, "I became convinced of the part played by mechanical causes in a large number of these patients." [1] Peacock also thought that heavy laborers showed diseases of the heart more often than others.[6] Dietlen called attention to the fact that soldiers had larger hearts than the general population, owing, he thought, to the severe military drills and enforced marches.[29] Schieffer, in several articles, pointed out that soldiers' hearts became larger after a year in service, especially if they had never done hard work in their civilian life [30, 31, 32, 33]; in addition, he observed that military bicycle riders of three or more years' service showed a definite increase in cardiac size. Furthermore, men in the heavier industries showed larger hearts than their fellows. Maase and Zondek,[34] and Klewitz,[35] in their more or less similar studies upon the military, found that infantrymen who had engaged in long marches had larger hearts than those who had not.

The athlete has also contributed his share to the controversy, since it was felt that the man engaging in competitive sports for any length of time, either as a professional or as an amateur, should certainly exhibit signs of chronic heart strain. Before discussing this particular phase of the problem, let us digress a bit and attempt to settle an issue that tends to add confusion to an already snarled subject. As previously stated, Gordon and Strong, as well as many others, found the hearts of rabbits and athletes to be either normal or slightly smaller than normal when checked after violent exertion.[13, 36, 37, 38, 39, 40, 41, 42, 43] As was to be expected, these findings have aroused much comment, speculation and free theorization. Albu, in studies made on wrestlers, discovered that at the end of one minute of the contest there was no change in heart size; at the end of five minutes the heart was smaller, and

at the end of 10 minutes it was larger.[44] Bruns' work showed that there was diminution in heart size following exertion, but that during the actual effort the results were uncertain, showing at times an increase and at other times a decrease in heart size.[45] Moritz tried to explain this phenomenon by the fact that the shortened diastole produced a lessened filling and hence a smaller heart.[37] Hoffman blamed the changing position of the diaphragm for giving a false impression of heart size, thus confusing the observer into believing that the heart size really changed.[36] The most plausible explanation, however, is that given by Bainbridge. He says that immediately after exercise the venous return to the heart is cut down most abruptly owing to the cessation of the muscle pumping action, whereas the heart rate remains elevated for some time, thereby creating a period during which the cardiac output exceeds the inflow, thus resulting in a diminution of heart size.[46] This explains quite clearly the reason why various workers have found the hearts to be smaller in subjects studied immediately after violent exercise. The cardiac dilatation during exercise, as pointed out by Albu,[44] and Bruns,[45] is physiological since the heart must, in an effort to increase its output per beat, dilate in accordance with the "law of the heart" to increase its contractile power. We may reasonably conclude, therefore, that the question of heart size immediately following exercise plays no part in our present discussion of heart strain.

We shall now return to the question of whether athletic pursuits over long periods of time are instrumental in the production of chronic heart strain. Deutsch and Kauf, who have done most extensive work on heart size in athletes, found that only oarsmen, swimmers and skiers showed cardiac enlargement of any appreciable degree. It is interesting to note that they found a familial tendency to larger hearts where they studied various members of the same family engaged in various sports for varying lengths of time. Those athletes who were observed for many years showed extremely diverse results. However, the authors did note that once the heart enlarged on exercise, even though it later became smaller, such hearts were more likely to become enlarged upon effort.[47] Again it must be pointed out here that such enlargement may have been only a work hypertrophy, for the figures given by Deutsch and Kauf do not point to true pathologic dilatations.

Since the old adage that "whatever the animals do must be natural," is accepted by many, it is of interest to look into some of the experiments dealing with them. Bergmann found that wild animals have larger hearts than household pets, owing, he thought, to the greater activity engendered by their wild state.[48] The birds that fly farther in their migrations have the bigger hearts, according to the researches of Parrot.[49] Grober compared the hearts of the wood hare, the wild rabbit and the pen rabbit. The wood hare had a heart that weighed three times that of the wild rabbit of the same body weight, and these hearts weighed more than those of the pen rabbits. In the duck family, the heart of the wild duck was heavier than that of the domesticated fowl.[50] Lastly, the frizzle fowl, that peculiar creature of an

even more peculiar name, with a markedly elevated metabolism and a heart rate of 100 beats or more per minute, more than that of ordinary chickens, also has a heart that is significantly heavier.[51] But here also the enlargement found may be explained upon the basis of physiologic work hypertrophy and need not be considered as truly pathologic or regarded as proof of damage to the heart by work.

In refutation of the chronic heart strain concept, we also possess a certain amount of valid work. Kahn, in a survey of the underlying factors of angina pectoris, restates the fact that those in strenuous occupations are less likely to experience attacks of angina pectoris, which he feels is owing to the fact that such hearts become accustomed to the strain of constant effort, whereas the hearts that have never been worked very hard are immediately injured when a sudden severe strain is put upon them.[52] Lewis, of course, is firmly arrayed against the concept of chronic strain. He points out that the enlargement seen in heavy laborers is entirely physiologic, due to a work hypertrophy which is not pathological, and that its counterpart is exhibited by the biceps and other muscles of the body as well.[16] Certainly, the marathon runner should be considered a heavy laborer from the point of view of chronic stress; yet, in studying a group of men who had been marathoners for from five to 15 or more years, Gordon could find no cardiac enlargement, using the cardiothoracic ratio or the transverse diameter figures as criteria for analysis.[53] Another argument against the chronic strain concept is the transcontinental derby. Farrel studied 23 runners three days after they had reached New York from Los Angeles. These men had averaged 41 miles daily for 84 consecutive days, yet only one of this group had an enlarged heart and that was the heart of a 64 year old, short, stocky individual who had been running for 40 years.[54] The cardiothoracic ratio of Danzer was used as a means of comparison.[54] When the tables of Bardeen were used five hearts showed greater diameters than the predicted ones.[54] Nevertheless, the authors concluded that the immediate effects of this long distance run were inconsequential.[54] It is well to recall that Deutsch and Kauf also found very few cardiac enlargements in their group of seasoned athletes.[47] Finally, White and Glendy, after a careful review of the literature, state that the constant strain of hard, physical work has never been proved to be the cause of myocardial disease.[5]

As we look back upon the material presented, we find that a preponderant volume of literature favors the concept of chronic heart strain as an entity, but a careful analysis of the literature makes it impossible for us to subscribe to the theory. In the first place, the etiology, pathology and symptomatology of the condition are practically those of arteriosclerotic heart disease, which we would expect to find in this age group anyway. Therefore, in any given case we are immediately confronted with the exceedingly difficult task of deciding whether the changes found are those owing to chronic heart strain or to arteriosclerosis from some other and entirely unrelated cause. This fact alone makes us wonder how many cases are labeled

chronic heart strain when they are merely showing to a lesser or greater degree the inexorable signs of "physiologic" sclerosis. Allbutt and Peacock based their impressions upon clinical observations over long periods of time.[1, 6] Keen observers though they were, one may nevertheless wonder how many of their cases were suffering from undiagnosed rheumatic fever, postinfectious myodegeneration, congenital heart defects, or from malnutrition and avitaminosis, all of which may eventually lead to the cardiac breakdown.

How then may we reconcile the facts that soldiers' hearts are larger than those of civilians, and messengers' hearts larger than those of ordinary soldiers, and the hearts of frizzle fowl larger than those of ordinary chickens? Lewis points out that the physiology of muscle is such that the cardiac musculature must hypertrophy with use within certain physiologic limits.[16] This will adequately answer all the questions raised in the introductory sentence of this paragraph. Furthermore, though the heart of the frizzle fowl is larger than that of the chicken, owing to its increased work, all frizzle fowl do not die of cardiac dilatation and failure, and neither do the wild rabbits or the soldiers. In other words, even though there is a work hypertrophy, subsequent dilatation and failure is not the rule nor is it even a common finding. Practically applied it means that the man who works hard all his life may have a heart that is larger than that of his desk-sitting contemporary, but this is entirely owing to a physiologic muscle development and not to a beginning myocardial damage with subsequent dilatation and failure.

Therefore, though the volume of words in support of chronic heart strain is preponderant, careful analysis of the material tends to invalidate most of it, leaving us with the logical conclusion that the concept of chronic heart strain is unsupported by scientific proof and as an entity is non-existent.

Somewhat timidly we are inserting the following paragraph of pure speculation, hoping that it will not confuse the picture which we trust has been somewhat clarified by this work.

Since the men in heavy industry are more likely to suffer an acute heart strain by the very nature of their work, we wonder how many of them do receive an acute strain which is overlooked and subsequently forgotten? Then, several months or years later, they suddenly begin to decompensate. How many of such instances, since there seems to be no other explanation, have been attributed to chronic heart strain? In other words, we raise the question as to how many cases of acute heart strain have gone unrecognized and the end results labeled chronic heart strain for the lack of a better appreciation of what had actually occurred. So rather than jump at conclusions and use the meaningless term of chronic heart strain in the face of a case of sudden decompensation in a heavy worker, it might be far wiser to look for an acute heart strain in his past history. *Not finding such a history, the presence of heart strain is to be absolutely excluded.*

We have attempted in this paper to establish only a basis for future work. No effort has been made to consider, as yet, the medico-legal significance of

our concepts or their application to industry. It has been our aim, so far, only to help the doctor diagnose and so treat the patient presenting himself with "a strained heart." The application of these principles to "heart strain" in industry is a question which is worthy of a separate discussion.

Summary

1. Heart strain is divided into acute and chronic types with definitions for each as a basis for discussion.

2. After a survey of the literature pro and con, it is felt that a clinical entity of acute heart strain can be justifiably established.

3. Theories as to the mechanism of acute heart strain are outlined.

4. The concept of chronic heart strain is considered to be too vague and uncertain and too lacking in confirmatory evidence to be established as an entity at all. It is felt that this term should be dropped since it is misleading as well as a misnomer.

5. The question of the heart in athletics is also considered from the point of view of heart strain.

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THE RELATIONSHIP OF UPPER RESPIRATORY INFECTIONS TO RHEUMATIC ACTIVITY IN CHRONIC RHEUMATIC HEART DISEASE*

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CLINICAL manifestations of rheumatic fever had long been known to follow infections of the upper respiratory tract. This sequence of events gave rise to the concept that these infections were etiological,[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12] particularly those having a predominance of hemolytic streptococci.[7, 8, 9, 10, 11, 12, 13] Several investigators, however, were unable to substantiate such a relationship even with regard to hemolytic streptococcus infections,[14, 15, 16, 17, 18, 19, 20] and some maintained that recurrences occurred more frequently without prior infections.[14, 15, 16, 19, 21, 22, 23, 24, 25, 26, 27] Furthermore, Bland and Jones [22] showed that the incidence of recurrences following operations, accidents and vaccine injections was similar to that occurring after upper respiratory infections. Although a relationship was highly suggestive, Swift [28, 29, 30] and others [31] were of the opinion that it still was not definitely proved. Swift [32] and others [33, 34] also demonstrated that a hypersensitive state existed in rheumatic subjects and that infections tended to increase it.[29, 30, 32, 35, 36, 37] The hypersensitive state, however, was not limited to bacterial filtrates, for the same reaction was observed to rabbit serum.[38] Coburn and Pauli,[10] the staunchest advocates of the etiological significance of hemolytic streptococcus infections, did not consider them the only factor underlying the development of rheumatic fever. Rinehart and his coworkers [39, 40] believed that vitamin C deficiency was the added factor, but Swift [28] could not prevent recurrences of the disease by active treatment with vitamin C. Rheumatic recurrences developing under such varied circumstances suggested the existence of an unrecognized factor or factors. It is obvious from these divergent views that the etiology of rheumatic fever is not yet definitely known.

It has been previously shown in this group of ambulatory rheumatic cardiac patients that active rheumatic infection was present in several cases and led to progressive cardiac damage and diminished cardiac reserve without the appearance of clinical manifestations of the disease; whereas, in others, a preëxisting active process was often noticed prior to the development of recurrences. These subclinical periods of rheumatic activity were recognized chiefly by the presence and persistence of leukocytosis.[41, 42] Be-

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cause of this experience it was deemed advisable to ascertain whether upper respiratory infections initiated rheumatic activity or complicated a pre-existing active process.

Seasonal Incidence of Upper Respiratory Infections. During the three-year period of observation 85 per cent of the patients experienced a total of 216 upper respiratory infections. The seasonal incidence showed a high prevalence in winter, a decline in summer and another period of high prevalence in fall (figure 1). These findings were in accord with those of Wilson et al.[14] and others observing non-rheumatic subjects.[43, 44, 45, 46]

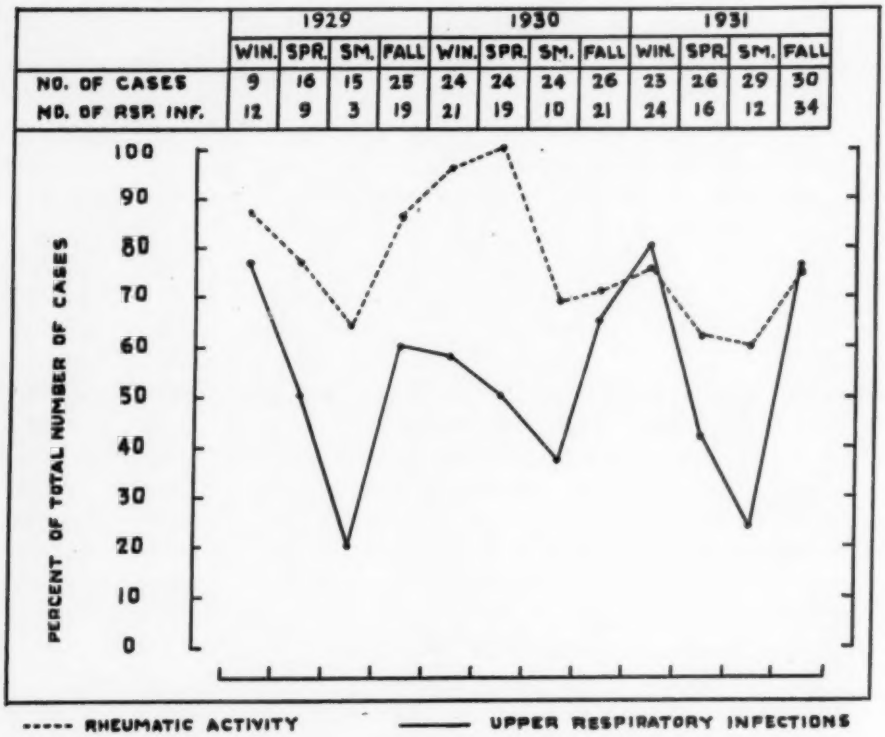

FIG. 1. Seasonal incidence of upper respiratory infections and rheumatic activity (first, second and third degrees, combined).

Upper respiratory infections per se are of doubtful significance as an etiological factor, since they occur with the same frequency in rheumatic and non-rheumatic subjects.

Seasonal Incidence of Upper Respiratory Infection and Rheumatic Activity. Rheumatic activity based on the classification previously proposed[42] was determined seasonally and compared with the seasonal incidence of upper respiratory infections (figure 1).

During 1929 the curves were parallel; during the winter of 1929-30 and spring of 1930 they diverged, becoming more or less parallel thereafter.

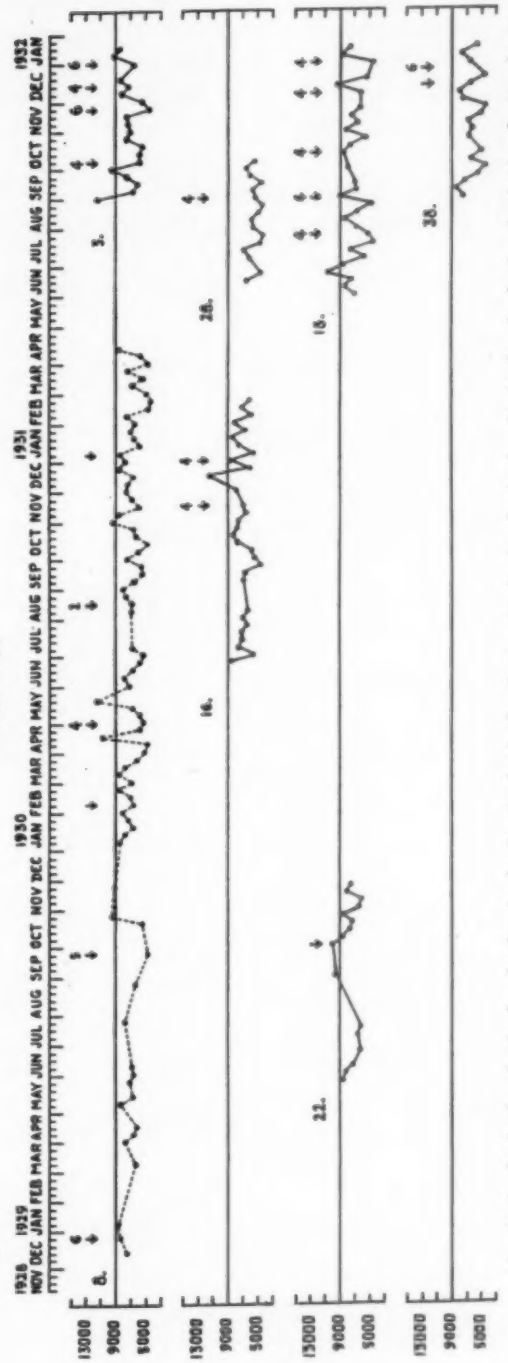

FIG. 2. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

The parallel course of the curves suggested a causal relationship, whereas the divergent course did not. From the fall of 1929 to the spring of 1930 rheumatic activity increased (80 per cent to 100 per cent), whereas upper respiratory infections dropped (60 per cent to 48 per cent). Furthermore, from the fall of 1930 to the winter of 1931 there was a marked increase of

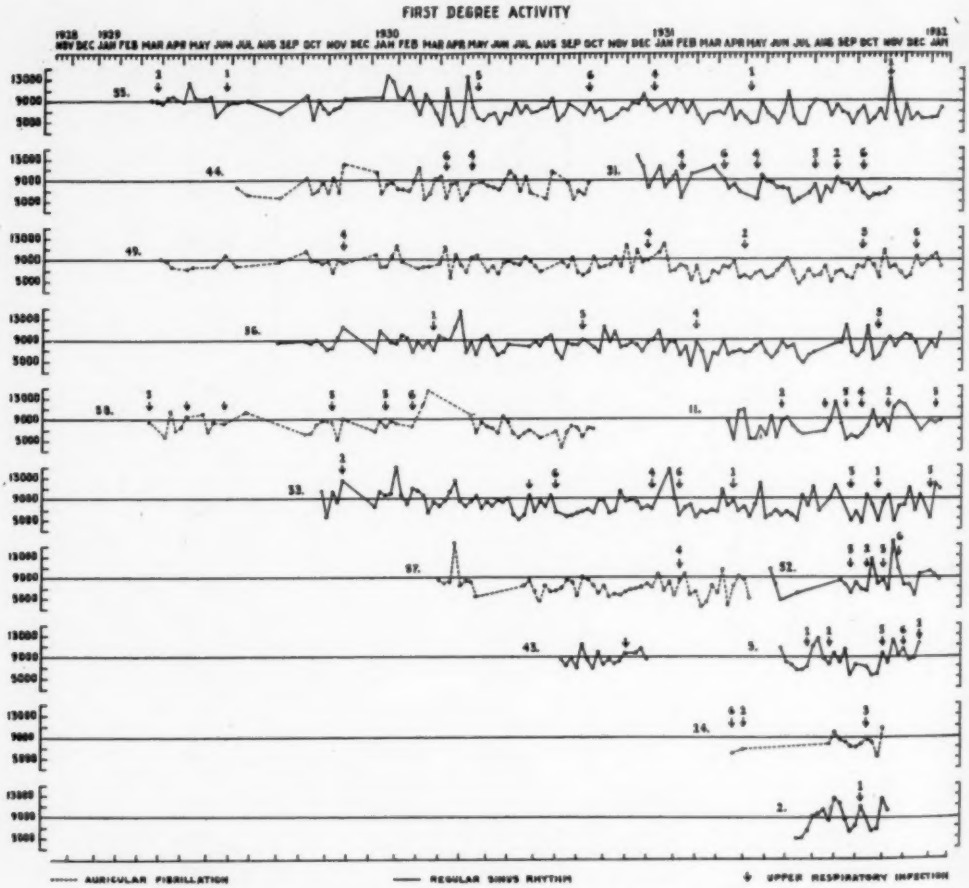

FIG. 3. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

upper respiratory infections (36 per cent to 78 per cent), with only slight increase of rheumatic activity (66 per cent to 72 per cent). In addition, the curves showed a seasonal incidence of rheumatic activity in excess of the seasonal incidence of upper respiratory infections, suggesting that rheumatic activity was present during some periods without prior infections. This was particularly apparent during the summer seasons.

A relationship between upper respiratory infections and rheumatic activity was not evident since the seasonal incidence of rheumatic activity did not vary directly with the seasonal incidence of upper respiratory infections.

The Relationship of Upper Respiratory Infections to Leukocytosis. Leukocytosis, often the only evidence of the presence and persistence of

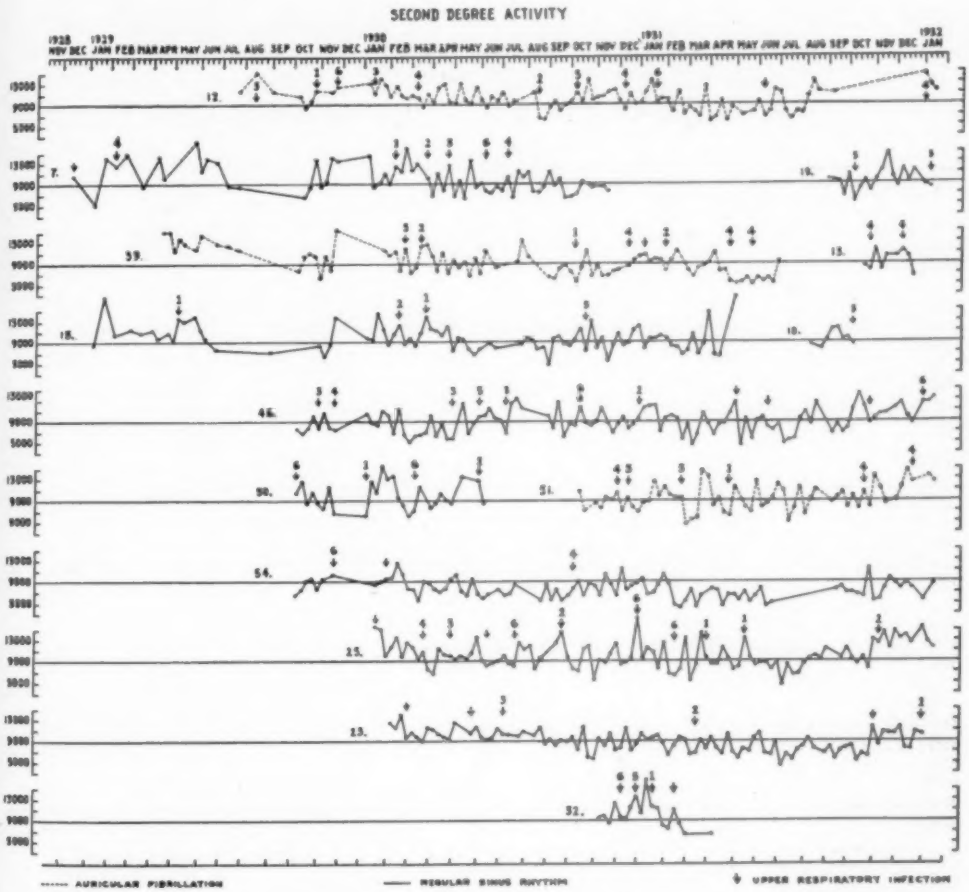
SECOND DEGREE ACTIVITY
1928 1929 1930 1931 1932
NOV DEC JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC JAN
AURICULAR FIBRILLATION
REGULAR SINUS RHYTHM
UPPER RESPIRATORY INFECTION

FIG. 4. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

rheumatic activity,[41] was examined with regard to its relationship to upper respiratory infections. The leukocyte curves of the cases were divided into four groups according to the classification of rheumatic activity (inactive, first, second, and third degrees).[42] The date of onset of upper respiratory infections was ascertained and recorded in relation to the weekly leukocyte counts.

Inactive (*figure* 2). Cases considered inactive during the period of observation failed to show leukocytosis prior to or following upper respiratory infections.

First Degree Activity (*figure* 3). The majority of upper respiratory infections in this group were not followed by leukocytosis. In some instances (Cases 49, 56, 58) leukocytosis was of short duration, whereas in others (Cases 2, 33, 43, 49, 56) it was present prior to the onset of the upper

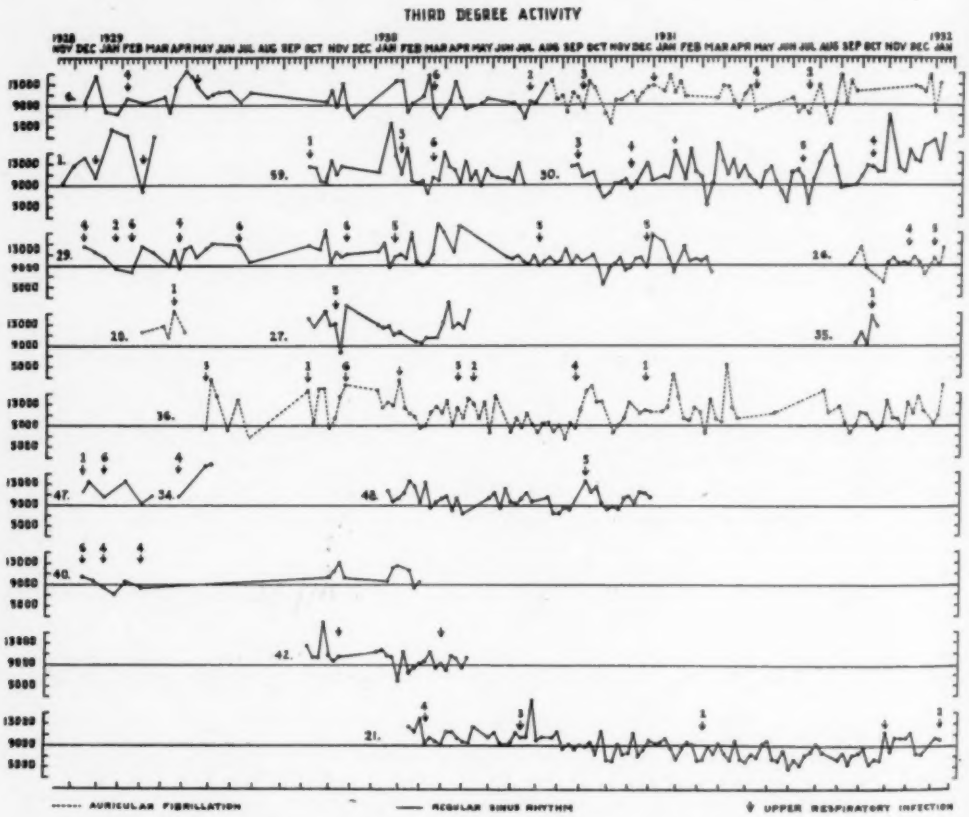
THIRD DEGREE ACTIVITY
1928 NOV DEC
1929 JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
1930 JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
1931 JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC
1932 JAN
AURICULAR FIBRILLATION
REGULAR SINUS RHYTHM
UPPER RESPIRATORY INFECTION

FIG. 5. Arrows designate upper respiratory infections in relation to weekly leukocyte counts. Arrows with numerals above designate upper respiratory infections and the number of days after the weekly leukocyte counts. Numerals at the beginning of each curve designate case numbers.

respiratory infections and became markedly elevated within one to three weeks after the infections (Cases 11, 33, 35, 49, 58). In some instances there was a series of upper respiratory infections associated with leukocytosis (Cases 5, 11, 52).

Second Degree Activity (*figure* 4) *and Third Degree Activity* (*figure* 5). Leukocytosis was a more or less constant feature in both groups and was usually present prior to the occurrences of upper respiratory infections.

In many instances leukocytosis was increased following upper respiratory infections, becoming markedly elevated within one to three weeks (Cases 32, 50, 54, second degree, figure 4; and Cases 1, 6, 29, 30, 36, 59, third degree, figure 5). Occasionally when the trend of the curve was downward toward normal, upper respiratory infections did not here influence its direction (Cases 25, 39, second degree, figure 4).

It was evident from these curves that upper respiratory infections were not followed by rheumatic activity in the inactive group, whereas, in first, second and third degrees, when rheumatic activity developed following upper respiratory infections, a preëxisting active process was usually present.

Discussion

It cannot be deduced from these observations that hemolytic streptococcus upper respiratory infections may not be an etiological factor in rheumatic fever; nor can we, on the other hand, disregard the importance of preëxisting subclinical periods of rheumatic activity, even with regard to recurrences following these specific infections. Many of our cases might have been considered inactive during various periods if it were not for the detailed method employed to detect rheumatic activity. A considerable number of the investigators of the etiology of rheumatic fever failed to determine whether or not their cases were active, but considered them inactive because they were symptom free and assumed that rheumatic activity began with the appearance of clinical manifestations of the disease.

Subclinical periods of rheumatic activity are probably much more prevalent than is generally realized. Not only do they exist in those already afflicted with the disease,[41, 42, 47] but the disease sometimes assumes this form in several sections of the country, being recognized only by the advent of cardiac lesions.[6, 48, 49, 50, 51, 52, 53, 54, 55] The appearance of clinical manifestations of the disease following operation, pregnancy, scarlet fever and other circumstances previously mentioned may also be explained on this basis; and perhaps subclinical rheumatic activity is the unknown factor mentioned by Coburn and Pauli [10] with regard to recurrences following hemolytic streptococcus upper respiratory infections.

A general idea of the extent of the prevalence of subclinical periods of rheumatic activity may be gleaned by a comparison of the curve of rheumatic activity of this group for the years 1930 and 1931 with that of Wilson et al., whose study covered this period.[14] Both investigations took place in New York City (figure 6). These authors observed 222 children between five and 15 years of age. The criteria of rheumatic activity in their group were clinical rheumatic recurrences such as polyarthritis, nodules, muscle and joint pains and acute carditis, whereas in this group the criterion was the classification based on the leukocyte count.[42]

The curves of the seasonal incidence of upper respiratory infections were also included to show the remarkable similarity of the seasonal incidence of rheumatic activity and upper respiratory infections of both groups,

particularly after the curve of rheumatic activity of our study had been reduced 60 per cent. Neither group showed a marked sudden rise of rheumatic activity in the winter and spring (figures 1 and 6) but appeared to fluctuate gradually from season to season.

The variation of rheumatic activity did not conform to the seasonal in-

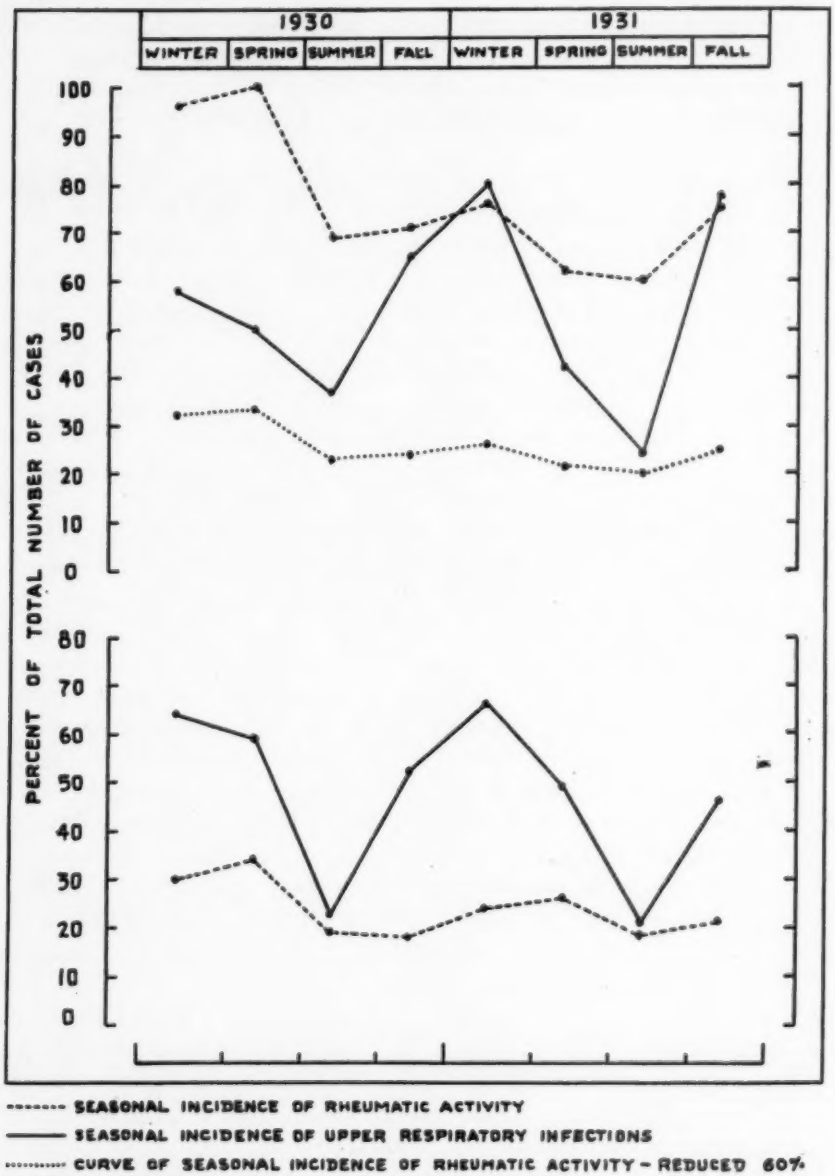

FIG. 6. A comparison of the seasonal incidence of upper respiratory infections and rheumatic activity. Upper group of curves, present study; lower group, that of Wilson et al.[14]

cidence of upper respiratory infections but rather to what seemed to be climatic influences. This would account for the lack of a uniform seasonal incidence of recurrences from year to year, since these factors also fluctuate from year to year in the North Temperate Zone. The only constant feature occurred during the summer seasons when rheumatic activity reached its lowest levels. One plausible explanation for the appearance of recurrences because of climatic factors would be complication of a preëxisting active process. Thus, the rheumatic activity in rheumatic cardiac patients who are transferred to warmer climates has a tendency to become quiescent, owing perhaps to milder climatic changes regardless of the incidence of upper respiratory infections.[43, 44, 56] Another explanation of the disappearance of recurrences would be the absence of hemolytic streptococcus infections, but this would not explain the recrudescences on returning to the Temperate Zone without contracting upper respiratory infections.[7]

The rôle of subclinical rheumatic activity as a phase of the disease has been somewhat underestimated. In this comparative analysis, 60 per cent more rheumatic activity seemed to exist in the subclinical form than was recognized by the clinical manifestations of the disease. This figure may appear high; yet 85 per cent of the cases in this study acquired rheumatic recurrences such as polyarthritis, nodules, acute carditis, muscle and joint pains at some time or other during the course of study,[41] conforming very closely to the pathological evidence of active disease as shown by Rothschild, Kugel and Gross.[57] These investigators have found active lesions in the myocardium in 80 per cent of the subjects fatally afflicted with rheumatic heart disease in the second and third decades. The absence of clinical manifestations of the disease is not sufficient to consider any case either quiescent or arrested unless carefully observed over an extended period. Subclinical rheumatic activity in rheumatic patients must be thought of in terms of years, not months.[41] Furthermore, if the data herein presented be true, how can there be any degree of certainty that upper respiratory infections preceding initial attacks of rheumatic fever are etiological? The same question can be raised regarding scarlet fever as an etiological factor. Rosenbaum,[58] studying 1770 cases of scarlet fever, observed 106 cardiac complications. These when broken down gave an incidence of valvular lesions of 1 per cent developing before and during the attack of scarlet fever, which was about the incidence observed in the general school population in New York City.[59]

It is, therefore, apparent that investigations of rheumatic fever based exclusively on clinical manifestations of the disease may be erroneous and misleading.

Summary

1. Eighty-five per cent of the cases of this group experienced a total of 216 upper respiratory infections. The seasonal incidence was similar to that observed in other studies of both rheumatic and non-rheumatic subjects.

2. A direct relationship between the seasonal incidence of upper respiratory infections and rheumatic activity was not evident.

3. The leukocyte curves of the cases were separated into four groups according to the classification of rheumatic activity and studied in relation to upper respiratory infections. In the inactive group upper respiratory infections were not followed by leukocytosis, whereas in cases showing activity of first, second and third degrees, when persistent leukocytosis followed upper respiratory infections, it was usually preceded by leukocytosis of varying periods indicating the existence of preëxisting rheumatic activity.

4. In many instances, particularly in second and third degree activity, leukocytosis became markedly elevated within one to three weeks after the upper respiratory infections, a latent period often mentioned prior to the appearance of recurrences. When this occurred preëxisting rheumatic activity was usually present.

5. Data are offered to suggest that approximately 60 per cent more rheumatic activity exists in the subclinical form than is recognized by clinical manifestations of the disease.

Conclusion

In this study evidence is presented to suggest that upper respiratory infections may complicate a preëxisting active rheumatic process rather than initiate it in cases developing rheumatic recurrences following these infections.

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PERIARTERITIS NODOSA; REPORT OF FIVE CASES *

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Since the first pathological description by von Rokitansky,[1] and the clinical and pathological correlation by Kussmaul and Maier,[2] more than 300 cases of periarteritis nodosa (panarteritis nodosa) have been described in the literature. The diagnosis during life has been rarely made, the great majority being discovered at the postmortem table. However, in more recent years the frequency of antemortem diagnoses has increased. We believe that, with proper appreciation of the pathology of the clinical picture, more cases of this affection can be recognized during the lifetime of the individual. We are reporting five cases that occurred in our service at the Cumberland Hospital during the past two years, four of which were diagnosed before the death of the individuals.

Case Reports

Case 1. A. M., aged 25 years, a beautician, was admitted to the Cumberland Hospital on July 18, 1935 with the chief complaint of abdominal pain and fever, both of one month's duration; tingling and numbness of the hands, forearms, and left foot of four days' duration. During the preceding month there were marked eructations of gas, loss of appetite, loss of weight (10 to 15 pounds), chills, and sweats.

The entire symptom-complex commenced six weeks before admission. At the onset, he felt chilly, his temperature was 102° and he sweated. A local physician was called in and made a diagnosis of la grippe. These symptoms persisted for seven days. After this he had a period of well-being that lasted for a week. At this time he developed an attack of hives over the extremities and trunk. This continued for four days and was attributed by his physician to the medication. At this time he began to notice pains in his feet accompanied by swelling and a temperature of 102°. The following day, abdominal cramps developed. These pains in the abdomen were "belt-like" and were almost continuous. The discomfort had no apparent relation to food or to the type of food taken. Accompanying, were daily attacks of vomiting of a watery, colorless to yellowish-green material. No blood was noted. When he did not vomit, gaseous eructations were annoying. Fever varied between 104° and 105°. All these symptoms persisted until four days before admission. At this time, he noted a numbness and tingling of the left hand and forearm up to the elbow, the right hand and lower half of the forearm, and the left foot.

Family History: Essentially negative.

Previous Personal History: Attack of hives at 7 years. Tonsillectomy in childhood. At the age of 10 years, he had a condition which was suspected of being typhoid but no definite diagnosis was made. He never smoked or drank alcoholic beverages, coffee, or tea.

Physical Examination: The patient was a poorly nourished, emaciated, white male, showing evidence of loss of weight and looking acutely ill. He was apprehensive,

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spoke incoherently. Skin was hot. Scalp, thinning hair. No tenderness over sinuses elicited; they transilluminated well. Pupils were regular, equal, and reacted to light and accommodation; conjunctivae pale. No petechiae noted. Tongue was dry. No petechiae noted on buccal mucosa. Dullness at base of right lung with diminished breath sounds. Point of maximal intensity of apex impulse in fifth left intercostal space 9½ cm. from midsternal line, soft systolic murmur at base, loudest at pulmonary area. Peripheral vessels appeared fibrotic. Liver and spleen not palpable. There was tenderness over the entire right half of the abdomen. Small, hard, movable lymph glands in both axillae; the right epitrochlear was palpable. No edema of extremities. Dorsalis pedis and posterior tibial arteries were easily palpable. Both forearms were extremely tender, and many purpuric spots noted on volar surfaces. Eyegrounds were essentially normal except for mild anemia of the retina.

Laboratory Studies: Blood Wassermann test negative (on two occasions). Spinal fluid was clear, pressure normal, 18 cells, slight increase in globulin. Wassermann negative. Colloidal gold, 0000000000.

Blood chemistry on admission: Blood sugar 116 mg. per 100 c.c.; urea nitrogen 42.5 mg. per 100 c.c.; creatinine 2.6 mg. per 100 c.c.

Blood chemistry three days before death: Blood sugar 142 mg. per 100 c.c.; urea N 46 mg. per 100 c.c.; creatinine 2.2 mg. per 100 c.c. Icterus index 4.1. Van den Bergh reactions negative. Three blood cultures were sterile. Widal negative. Sputum negative for tubercle bacilli on two occasions. Cultures of urine negative for organisms.

Urine on admission: Specific gravity 1.014. Faint trace of albumin, 30 red blood cells per high power field. Four other specimens of urine showed increasing quantities of albumin, numerous red blood cells, and both hyaline and finely granular casts.

Blood count on admission: white blood cells 27,200, red blood cells 2,640,000, hemoglobin 40 per cent, polymorphonuclear neutrophiles 79 per cent, monocytes 3 per cent, lymphocytes 18 per cent, eosinophiles 0.

Red blood cells were normal in size and shape, but showed marked central pallor. White blood cells were all mature. Blood sedimentation time (18 mm.) 10 minutes.

Blood count two days before death: red blood cells 2,840,000, white blood cells 15,100, monocytes 11 per cent, lymphocytes 14 per cent, eosinophiles 0, polymorphonuclear neutrophiles 75 per cent.

Blood pressure 140 mm. Hg systolic and 68 mm. diastolic; 132 mm. systolic and 74 mm. diastolic.

Roentgen-ray of the chest showed the heart to be somewhat enlarged to the left with a bulge in the left auricular pulmonic angle. There was no evidence of parenchymal or pleural involvement.

Flat plate of the abdomen showed marked gaseous distention.

Course: During the entire stay of seven days at the hospital, the temperature varied between 101° and 103°; the pulse was rapid and not proportional to the temperature. On the fifth day after admission, tremor of both hands and legs developed, and the abdominal pain and tenderness persisted. He often complained of blurring of vision and some haziness. Mentally he was dull and had to hesitate and think before understanding questions asked. On the morning of the day of his death (5:00 a.m.), he suddenly became cool and clammy, with cold perspiration, and the tremors of hands and feet increased. Respirations were of the Biot type. Temperature at that time was 101°, pulse 120. He coughed considerably, expectorating blood-tinged sputum. He voided smoky-red urine. This state of affairs persisted until the time of his death.

Necropsy, Case 1. General: The body is that of a well-developed and under nourished young adult white male. The skin is fair, and the hair is straight and dark. There is slight icterus of skin and conjunctivae. A petechial hemorrhage is observed on the conjunctiva of the left lower lid. Purpuric spots are present on the

volar surfaces of both arms. A "splinter" hemorrhage is present under the nail of the left middle finger.

Cavities: Peritoneal cavity contains 350 c.c. of clear yellow fluid. Right pleural cavity contains 200 c.c. of clear yellow fluid. Pericardial fluid is slightly increased in quantity.

FIG. 1. High power magnification of a characteristic section of lung of case 1. Note small artery (*A*) the wall of which (*B*) is infiltrated with leukocytes, the infiltrate extending into adjacent perivascular structures (arrow).

Cardiovascular system: Heart weighs 390 gm. Some of the epicardial vessels are occluded by thrombi and present nodular thickenings (see visceral arteries). The ventricles are moderately dilated and the myocardium slightly hypertrophied. A subendocardial fibrous nodule is found on the atrial surface of the posterior mitral leaflet.

The aorta and other peripheral vessels including veins are in an excellent state of preservation, presenting only a very occasional area of perivascular round cell infiltration of the adventitia.

Visceral arteries of the various organs described below show the following changes occurring either separately or in combination:

(*a*) intimal proliferation with or without infiltration of portions or of the entire vessel wall by polynuclear, mononuclear and numerous eosinophilic leukocytes;
(*b*) medial necrosis of varying degree;
(*c*) aneurysms, single or multiple;
(*d*) thrombi occluding vessels;
(*e*) recanalization of thrombi;
(*f*) fibrous tissue replacement of thrombi.

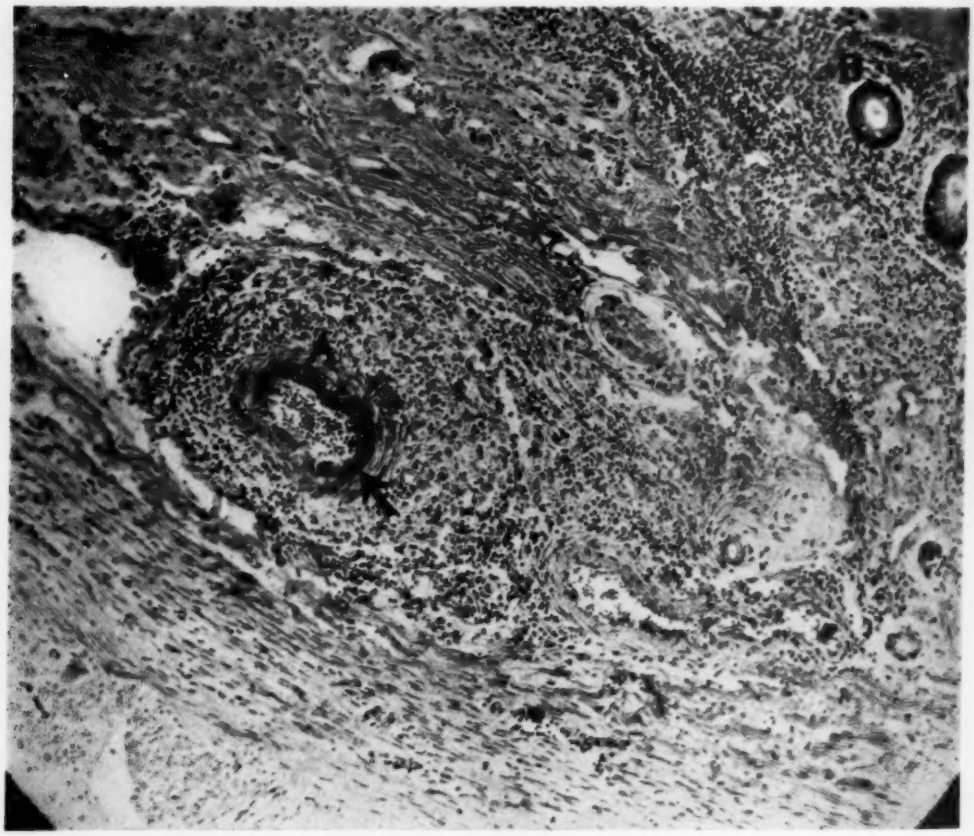

FIG. 1*A*. Cross section of the appendix of case 1, showing the characteristic and prominent medial necrosis (arrow) as well as acute inflammatory infiltrate in the wall of a small artery (*A*) in the muscularis. Note the infiltrative process extending into the mucosa (*B*). (180X).

Respiratory System: The pulmonary arteries are markedly involved in the acute phase of the inflammatory lesions described above (figure 1). Many of the vessels are occluded by thrombi, resulting in hemorrhagic infarctions which extend to the pleural surface. The posterior borders of the lower lobes also contain patchy areas of gray hepatization. Many alveoli are filled with "heart failure" cells.

Gastrointestinal System: Gross lesions are not demonstrable anywhere along the

tract, although microscopically extensive acute arteritic changes are found in the mesenteric vessels which supply their respective segments of gut. In the appendix, the submucosal as well as the serosal vessels show acute arteritis in its exudative form, with pronounced medial necrosis, producing the characteristic picture of the acute phase of the disease (figure 1*A*).

Biliary system: Liver weighs 1970 gm. Red mottling of hepatic parenchyma is seen through a smooth Glisson's capsule. These areas of discoloration are produced by fresh thrombotic occlusion of branches of the hepatic artery (figure 2). All stages

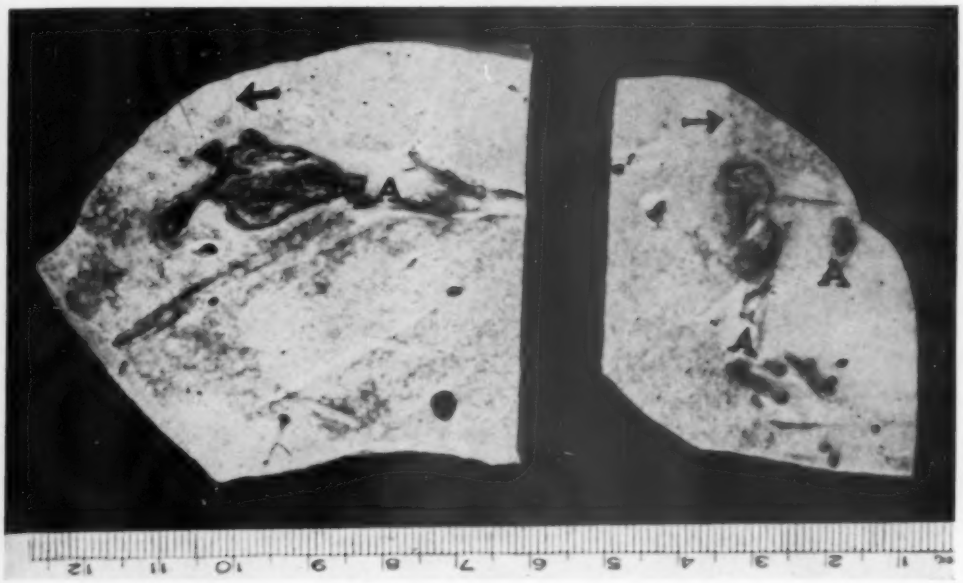

FIG. 2. Cut surface of liver of case 1, showing thrombus in branches of hepatic artery (*A*) as well as yellow and red mottling of parenchyma. The arrows point to pyramidal, red and gray peripheral infarcts.

of periarteritis, acute as well as healed, and the changes in the hepatic parenchyma secondary to the vascular lesions are demonstrable in this organ. Most of the liver lobules present periportal infiltration, hemorrhagic extravasation, compression of bile ducts, bile retention, foci of fat replacement, and various degrees of fibrosis.

The gall-bladder is filled with dark fluid bile and the wall is thickened by an acute and subacute periarteritic process. At the tip of the fundus, there is a saccular dilatation of the wall, about 2 cm. in diameter.

Pancreas weighs 120 gm. and presents acute and subacute periarteritis, with but slight parenchymal changes.

Spleen weighs 190 gm. The capsule is smooth and the corpuscles are prominent. Arterial lesions similar to those described in the liver are found in abundance. Many of the central arterioles of follicles show necrosis of their walls. Fibroblasts are seen radiating from the central arteriole and replacing the lymphoid cells of many follicles.

Urinary system: The right kidney weighs 125 gm. and the left 225 gm. Capsules strip with difficulty, exposing numerous yellow, gray and red areas of discoloration due to old anemic and recent hemorrhagic infarcts. The cut surfaces disclose numerous arteries which are filled with thrombi some of which occupy aneurysms, leading to areas of infarction. Microscopically, all stages of periarteritis are demonstrable

although the acute phase is most prominent (figure 2*A*). Many glomeruli are necrotic or completely replaced by fibrosis and hyalinization. Tubules are distorted, many dilated and filled with hemoglobin, cellular, or hyalin casts. The walls of the ureters present nodular thickenings due to thromboarteritis, in areas producing partial obstruction to the lumen.

FIG. 2*A*. Section of kidney of case 1, showing a characteristic acute arteritis. Note narrowed lumen (*A*), also the infiltrate, edema and medial necrosis (*B*) of the vessel wall. The polynuclear cell infiltration is most marked in the outer coats (*C*) of the vessel (60 ×).

Endocrine system: Thyroid shows increased colloid secretion. Thymus is absent. Adrenals weigh 15 gm. The periadrenal vessels show acute and subacute arteritis. The vessels of the parenchyma proper show only slight or no involvement. Pituitary shows a comparative increase of chromophile cells.

Lymphatic system: The mesenteric and preaortic nodes show extensive acute periarteritis. The exudative process appears to be most marked in the vessel wall, where aneurysm or branching occurs.

Skeletal system: The orbital muscles of the left eye present a mild periarteritis.

Central nervous system: Brain weighs 1555 gm. Some of the superficial meningeal vessels contain thrombi. The left carotid artery contains a thrombus which extends into the ophthalmic and cerebral branches. The anterior superficial portion of the left frontal lobe presents an area about 2 cm. in diameter, in which are found multiple minute thrombi and petechial hemorrhages. This area merges with an irregular area of softening which extends posteriorly through frontal and parietal lobes of the postcentral gyrus. Microscopically, this area of softening shows white cell thrombi occluding many of the arterioles and disintegrated cerebral tissue which is adjacent to these vessels. The medulla shows dilated Virchow-Robin spaces containing red cells.

Spinal cord shows occasional areas of hemorrhagic extravasation into the Virchow-Robin spaces of the anterior horns.

Anatomical Diagnosis: (1) Panarteritis nodosa; (2) multiple petechial hemorrhages and visceral infarcts; (3) cardiac hypertrophy and dilatation; (4) anasarca; (5) lobular pneumonia; (6) icterus.

Summary, Case 1: Male, perfectly well until seven weeks before death, commenced with chilly sensations, fever, sweats lasting seven days, followed by a period of good health for one week. He then had an attack of urticaria with a recurrence of fever, pain and swelling of the feet, continuous abdominal cramps, and later, numbness and tingling of both upper extremities and left foot. The outstanding findings were fever (101° to 103°), loss of weight, anemia, abdominal tenderness, extreme tenderness of muscles of forearms. The laboratory findings were anemia, hemoglobin 40 per cent, leukocytes varying between 15,000 and 27,000, no eosinophilia, polymorphonuclear neutrophiles predominating, 75 to 79 per cent; moderate nitrogen retention, and persistent urinary findings of albumin, numerous red blood cells, hyaline and granular casts.

Autopsy revealed definite changes of periarteritis nodosa involving the vessels of the lungs, mesenteric vessels, appendix, liver, gall-bladder, pancreas, spleen, kidneys, periadrenal vessels, the lymphatic nodes, brain and nervous system.

Case 2. M. R., aged 46, was admitted on December 20, 1935 and died on December 28, 1935.

Chief complaints on admission were precordial pain, shortness of breath, and swelling of both legs of one year's duration. In addition to the above symptoms, she complained of pain in the neck of three weeks' duration. This patient was perfectly well until one year before admission. She began to notice shortness of breath increasing in frequency and severity. In addition, she had severe attacks of nocturnal dyspnea. Associated with these symptoms, she had attacks of palpitation, precordial pain, and swelling of both legs. For the past three or four weeks, she complained of pain in the neck radiating down both arms to the finger tips. The right arm and right lower extremity became weaker rather suddenly one week before admission. During the past year she knew that she had sugar in her urine, and that her blood pressure was elevated. She was not on a restricted diet nor was she receiving any insulin.

Family and personal history were essentially negative. She was never ill except for her present disability. Denied gonorrhea and syphilis. She did not smoke, and partook moderately of alcoholic beverages.

Physical examination: Obese colored female who was dyspneic and orthopneic. Pupils were equal, reacted to light and accommodation, conjunctivae of fair color. No petechiae were noted. Examination of fundus revealed tortuous vessels, but no hemorrhages or exudates. There was no evidence of any cranial nerve palsies. Ears and nose were negative. There were many carious teeth. There was no rigidity of the neck, nor were any enlarged glands noted. Heart showed the point of maximal impulse to be in the sixth left intercostal space within the midclavicular line. Sounds

were of fair quality with regular sinus rhythm. The pulmonary second sound was little louder than the aortic second. No murmurs were heard. Dullness of both lung bases with many fine moist râles. Liver enlarged to four fingers below the costal margin. Spleen was not palpable. There was a hard immovable mass that extended from two fingers below the umbilicus into the pelvis. Pelvic examination revealed this mass to be connected with the uterus (fibroid). Sacral edema was present. Both lower extremities were edematous. The right upper and lower extremities showed definite impairment of motor function and diminished reflexes. Rectal examination showed nothing of importance.

Laboratory studies: Blood Wassermann test negative. Urine revealed glucose 2 per cent, no acetone, specific gravity 1.020, no albumin, no casts, several red blood cells per field.

Blood examination: White blood cells 9,200, red blood cells 4,300,000, polynuclears 72, lymphocytes 28, hemoglobin 85 per cent.

Chemical examination of the blood on December 23 showed: Sugar 350.8 mg. per 100 c.c., urea nitrogen 25.8 mg. per 100 c.c., creatinine 1.7 mg. per 100 c.c., uric acid 4.4 mg. per 100 c.c., cholesterol 245 mg. per 100 c.c., cholesterol esters 47 mg. per 100 c.c. On December 26, examination showed: Sugar 339 mg. per 100 c.c., urea nitrogen 38.4 mg. per 100 c.c., creatinine 1.5 mg. per 100 c.c., uric acid 5.3 mg. per 100 c.c.

Clinical course: During her stay at the hospital, her pulse was relatively rapid in relation to the temperature curve, the pulse varying between 100 and 130, the temperature between 99° and 102°. Her blood pressure, 190 mm. Hg systolic and 100 mm. diastolic on admission, varied between 190 and 240 systolic, and 100 and 112 diastolic. In spite of the therapy, the patient continued in congestive heart failure, becoming irrational the day before death. At this time there was considerable drooping of the right side of the mouth, and the tongue deviated to the right. There was complete paralysis of the right lower extremity and marked weakness of the right upper. There was no change in the cardiac findings. There was an increase of râles in both bases of the lungs. The next day the patient died.

Necropsy, Case 2. General: The body is that of a well developed and well nourished negress.

Cavities: Pleural cavities contain numerous fresh adhesions.

Cardiovascular system: Heart weighs 490 gm. The right atrium and ventricle are dilated and the left ventricle is slightly hypertrophied. The coronary arteries show moderate sclerosis and the myocardium presents considerable fibrosis. The mitral valve shows fibrosis of its free margin.

Respiratory system: The trachea and bronchi are congested. The lungs show a healed tuberculous lesion in the left apex and hypostatic congestion with irregularly distributed areas of emphysema in the rest of the parenchyma.

Gastrointestinal system: The entire tract shows congestion of the lining. Pancreas weighs 75 gm. and shows a moderate amount of fibrosis. Spleen weighs 120 gm. and also shows a moderate amount of fibrosis.

Biliary system: Liver weighs 1700 gm. and shows considerable cloudy swelling. The periportal tissues are infiltrated with polynuclear and lymphoid cells.

Gall-bladder contains viscid bile. Its wall is thickened by congestion and infiltration with polynuclear and round cells. The arteries present characteristic medial necrosis with peri-, as well as panarteritis (figure 2*B*).

Kidneys: The capsules strip with difficulty revealing occasional cortical cysts. The glomeruli and arterioles of the cortex show the characteristic changes of accelerated arteriolosclerosis. Many of the glomeruli are completely hyalinized and many of the arterioles show almost complete obliteration of lumina by the intimal proliferation. Arcuate arteries, and occasionally those of lesser as well as smaller

caliber show medial necrosis and infiltration characteristic of periarteritis nodosa (figure 2*C*). The calices and rest of the pelvis are markedly dilated.

Ureters are distended due to uterine fibroids which impinge upon the ureteral entrance into the bladder. The wall of the right ureter also presents characteristic periarteritis.

FIG. 2*B*. High power magnification of gall-bladder of case 2 showing two muscular branches of the cystic artery on cross section (*A*). Note the medial necrosis (*B*) and intense polynuclear and eosinophilic infiltrate in adventitia and adjacent perivascular tissue (arrows).

Uterus contains multiple intramural and one large subserous fibroid which distort the organ and press upon the bladder and ureters.

Ovaries are sclerotic and atrophied.

Endocrine system: Adrenals show considerable hemorrhagic extravasation into the parenchyma.

Anatomical diagnosis: (1) Nephrosclerosis (accelerated); (2) panarteritis nodosa; (3) cardiac hypertrophy and dilatation; (4) chronic passive congestion of viscera; (5) fibromyomata uteri (with ureteral obstruction); (6) hydroureter and hydronephrosis.

FIG. 2C. High power magnification of a representative portion of kidney of case 2, showing a small artery (*A*) with the characteristic necrosis of its medial wall (*B*) and acute inflammatory infiltrate in and about the wall of the vessel (arrow).

Summary, Case 2: This patient was a known diabetic with hypertension. There was gradual progressive heart failure with anginal symptoms of one year's duration. The physical findings were all in agreement with progressive heart failure: orthopnea, large heart, basal râles, large liver, sacral and leg edema. At the end, she developed a right hemiplegia. Laboratory examinations revealed glycosuria, a few red blood cells in the urine; hyperglycemia, 339 and 350 mg. per cent; hemoglobin 85 per cent, white blood cells 9,200.

Autopsy revealed panarteritic changes in the arteries of the gall-bladder and kidneys (permission for opening the cranial cavity was not obtained). The diagnosis of panarteritis nodosa was not made until after the postmortem microscopic study.

Case 3. F. A., aged 55, Italian butcher, was admitted to the service of Dr. J. J. Guttman at Cumberland Hospital on November 9, 1936 and died on April 18, 1937. Chief complaints on admission were chills, fever, and pain in both legs of 11 days' duration. Eleven days before admission he had a sudden chill followed by fever, and after the first chill he had three more at irregular intervals.

Two days after the initial chill, pain and weakness of both legs appeared and were of such severity that he had to remain in bed. However, on close questioning the patient admitted having had a sore throat two weeks prior to the onset of the above symptoms.

Family history showed nothing of importance. He was a moderate drinker and commenced to smoke three years previously. Nine years previously, he was in bed with thrombophlebitis involving both lower extremities. At the age of 17, he contracted malaria in Italy, was treated with quinine, completely cured, and has had no recurrence since.

Physical examination: White, well-nourished male, perspiring profusely, appeared quite ill. The right pupil was irregular and smaller than the left, but both reacted to light and accommodation. No conjunctival petechiae were noted. Many carious teeth were present. Tongue was coated and pharynx quite injected. Chest was emphysematous in shape with inconstant moist räles at the bases of both lungs. The point of maximal impulse of the heart could not be made out. The borders could not be definitely made out. The sounds were regular and of good quality. There were no murmurs. The aortic second sound was louder than the pulmonic second sound. The liver and spleen were not palpable. However, marked tenderness was elicited over the right lower costal margins anteriorly and posteriorly. There was no edema of the extremities nor was there any tenderness in the calf muscles. Complete neurological examination revealed nothing of note. The left epididymis was tender, painful, and definitely thickened.

Laboratory studies: Urine showed albumin 1 to 2 plus with finely granular casts during his entire stay. When jaundice appeared, bile was present. Examination of the urine for arsenic, lead, leucine and tyrosine crystals, and tubercle bacilli was negative. Blood Wassermann was 2 plus on admission, but subsequently repeated Wassermann tests, as well as the provocative test, were negative. Spinal fluid Wassermann was negative. Colloidal gold curve 1122110000. Gonococcus complement fixation was negative. Repeated blood cultures (five) were negative. Agglutination tests for typhoid, paratyphoid, undulant fever, suipestifer, and tularemia were negative. Stools were consistently negative for ova, parasites, and *B. typhosus*. Mantoux test was negative. Sputum was negative for tubercle bacilli and spirochetes.

Chemical examination of the blood: Sugar 125 mg. per 100 c.c., urea nitrogen 24 mg. per 100 c.c., creatinine 1.7 mg. per 100 c.c. cholesterol 180 mg. per 100 c.c., cholesterol esters 40 mg. per 100 c.c., icterus index 9.3. *March 19.* Regular sinus rhythm, rate 110. $QRS_{1, 2, 3}$ slurred; QRS_3 inverted, low voltage. T_1 diphasic, T_3 depressed.

Roentgen-ray of chest: November 10 and 14, December 17, and February 17 negative. March 18: Heart is aortic in configuration, cardio-thoracic ratio 50. An axillary band of density with a more or less sharply defined inner border extends from the base of the right lung field toward the sixth intercostal space posteriorly. The right diaphragmatic leaf is visualized disappearing within the opacity which obscures the base. There is a thickening of the interlobar fissure between the right upper and middle lobes. There is a very marked accentuation of the pulmonary striation, which would indicate the presence of an engorgement of the lesser circulation. The axillary

band of density on the right side is indicative of the presence of fluid in the pleural cavity of the right hemithorax.

Flat plate of abdomen: November 10 negative. November 14: The right ilio-psoas shadow is indistinctly visualized. The left is not visualized at all. Both kidneys are very indistinctly outlined. The lower pole of both kidneys is approximately at the level of the transverse processes of the third lumbar vertebra. Evidence of osteo-arthrosis in the form of lipping is noted at the upper and lower articular surfaces of the third lumbar vertebra.

Kidney function tests: specific gravity varied between 1.005 and 1.012, phenol-sulphonphthalein excretion 27.5 per cent in two hours. Bromsulphalein and galactose tolerance tests revealed normal liver function. The congo red test was normal. Sedimentation time varied between 18 and 37 minutes.

Blood examination:

	11/9	11/20	12/5	12/27	1/11	2/3	2/16	3/17
White blood cells	14,650	12,000	7,100	6,800	6,200	4,200	3,900	7,250
Red blood cells, millions	4,8	5	4,22	3,4	3,8	2,6	2,75	3,18
Hemoglobin, per cent	115	85	62	56	65	60	55	52
Polynuclear neutrophiles	86	83	74	70	71	74	80	71
Lymphocytes	14	12	26	30	18	26	18	14
Monocytes		5			4		2	7
Basophiles					1			2
Eosinophiles					4			6
Turck cells					2			

Fragility test of red blood cells normal.

Smear for malaria negative.

Electrocardiograms: *November 21.* Sinus rhythm with pulsus trigeminus. QRS_3 inverted. Premature contractions from right ventricle, one interpolated beat from left ventricle. $T_{1,2}$ isoelectric; T_3 inverted. *January 8.* Regular sinus rhythm, rate 140. P_3 isoelectric. QRS_3 inverted. T_1 inverted; T_2 diphasic.

Intravenous pyelogram: (January 22) Both ilio-psoas muscles are sharply outlined on all the exposures. The kidney shadows are visualized on all the exposures. The left kidney takes the dye better than the right one, and has a bifid pelvis. The right kidney pelvis cannot be made out because of poor concentration of the dye. Neither of the calyces on the left or right side is well visualized and no statement can be made as to the presence of any blunting of the lesser calyces. The right ureter shows a spindle-shaped dilatation about 2 cm. above the ureteropelvic junction. This is visualized on all the exposures.

Roentgen-ray of the left forearm and right leg showed no radiographic evidence of sclerotic changes in the vessels.

Clinical course: The temperature of the first week varied between 103° and 104°; for the next five weeks, 101° and 102°; and the rest of the stay between 99° and 101°, except for the last five days, when it reached subnormal on numerous occasions. The pulse varied between 80 and 120 until three weeks before the end. At this time there were periods when it averaged 130. The blood pressure was 106 systolic and 68 diastolic on admission, continued at this level until the end of the seventh week when it rose to 154 systolic and 100 diastolic, and remained elevated until death. On November 13, he developed transient icteric sclerae associated with epigastric pain and tenderness which disappeared in a few days. On November 21, the pulse became irregular, heart sounds poor, and electrocardiogram showed pulsus trigeminus. On November 25, the extremities became weak and the patient showed positive left Babinski, Oppenheim and Gordon reflexes. On December 7, the spleen was felt. On December 16, position and vibration sense was lost and knee jerks were absent. On January 6, 1937, he developed paroxysmal dyspnea. On January 9, bilateral foot drop appeared. On February 10, the liver was palpable. Both liver and spleen became

progressively larger. On February 16, purpuric spots developed over the legs and gradually disappeared in a few weeks. Weakness became progressively worse. There was progressive atrophy of the muscles, particularly of the extremities, with trophic changes of the hands, arms, and soles of the feet. The patient lost 50 pounds during his stay at the hospital. Signs of heart failure appeared. Patient became irrational and died one week later.

Necropsy, Case 3. General: The body is that of a well developed and fairly nourished white male about 55 years of age.

Cavities: The right pleural space is obliterated by adhesions and enclosed collections of serous fluid. The left contains air and about 1200 c.c. of fluid and clotted blood.

Cardiovascular system: Heart weighs 475 gm. The apex is rounded. The epicardium and endocardium are normal. The myocardium is thickened, and on section shows pale gray streaks. Microscopic examination reveals fibrous replacement, interstitial edema, and cloudy swelling of the muscle fibers. The mitral valve shows fibrous thickening along the closing margin. There is no other more definite pathologic evidence of recent or old rheumatic involvement.

Respiratory system: Trachea and bronchi show an intense acute inflammatory process in the mucosa. The right middle and lower lobes of the lung show a marked broncho-pneumonic process with suppurative bronchiolitis. The left lower lobe is the seat of recent hemorrhagic infarction. Some of the arterioles show inflammatory changes in their walls.

Digestive system: Esophagus shows marked changes in the serosal arterioles, characterized by medial degeneration, partial occlusion of the lumina by thrombi, aneurysmal dilatation and cellular infiltration of the walls.

Small and large intestines show marked submucosal congestion. The splenic flexure of the colon contains submucosal venous thrombi and small diverticula. One section of colon shows metaplasia of lining from columnar to squamous cells.

Spleen weighs 360 gm. and shows congestion.

Pancreas weighs 90 gm. One section shows a small artery the wall of which is the seat of necrosis (especially of the medial coat) with polynuclear leukocytic infiltration. There are many vessels showing aneurysmal dilatation. Some also show fibrosed, hyalinized or recanalized thrombi. These stigmata of healed panarteritis are present throughout.

Biliary system: Liver weighs 1325 gm. The capsular surface is partly nodular and shows depressed scars, hemorrhagic zones and dilated spaces which, on section, are found to be filled with blood and bile. Microscopic examination reveals loss of normal architecture and cirrhosis. Many of the ducts are dilated and filled with bile. The vascular changes are similar to those described in the pancreas. Recent hemorrhagic infarctions are present in abundance.

Gall-bladder and cystic duct are normal.

Common bile duct, its tributaries and ampulla of Vater are all dilated.

Urinary system: The right kidney weighs 100 gm. and the left 160 gm. The cut surface reveals many areas of recent and old infarction (figure 3). Microscopic examination shows advanced changes involving the arteries and arterioles. These changes consist of aneurysmal dilatation or obliteration of the lumina by organized, hyalinized or recanalized thrombi. Various degrees of glomerular and interstitial fibrosis are also present.

Reproductive system: The left testis is atrophied and the epididymis is thickened (figure 3). The vessels in the thickened tunica albuginea show arteritic changes similar to those described in the other viscera. The parenchyma of the gland contains rests of chromaffin cells.

Prostate shows a glandular hyperplasia and an increase in the fibrous stroma. The vascular changes are similar to those observed in the other organs.

Skeletal system: The intercostal muscles are opaque, pale gray in color and microscopically show Zenker's degeneration.

Anatomical diagnosis: (1) Panarteritis nodosa; (2) multiple visceral infarction (renal, pulmonary, hepatic); (3) cirrhosis of liver (atypical, periportal); (4) biliary obstruction (intrahepatic); (5) splenomegaly; (6) myofibrosis cordis; (7) cardiac hypertrophy and dilatation; (8) bronchopneumonia (terminal); (9) hemopneumothorax; (10) atrophy and chromaffin rests of testis; (11) metaplasia of intestinal mucosa; (12) pleural adhesions (fibrous); (13) diverticulosis coli; (14) accessory spleen.

FIG. 3. Cut surfaces of kidney and testis of case 3. Arrows point to infarcts in both organs.

The testis (*A*) is partly atrophic and the epididymis (*B*), as well as the tunica albuginea (*C*) is markedly thickened by fibrous tissue.

Summary, Case 3: Adult male, 55 years of age, was admitted to the hospital with a history of chills, fever, and pain in the legs of 11 days' duration, all following a sore throat two weeks previously.

Repeated examinations during his five months' stay at the hospital revealed a well-nourished male with progressive cachexia, cardiac irregularities and weakness, transient epigastric tenderness, hepatic and splenic enlargement, bilateral foot drop, atrophy of the muscles, particularly of the extremities, purpuric spots over the legs, trophic changes of the hands, arms, and soles of the feet, transient icterus, and neurological abnormalities. Fever, anemia, and hypertension were present. There was moderate nitrogen retention in the blood with persistent albumin and casts in the urine.

Autopsy revealed characteristic changes of panarteritis nodosa involving the vessels of the lungs, esophagus, intestines, pancreas, liver, kidneys, testes, and prostate.

Case 4. R. T., aged 29, chauffeur, born in British West Indies, admitted to Medical Service, Cumberland Hospital, April 29, 1937, died June 11, 1937.

Chief complaint on admission was pain in legs. Three and a half months before admission, he had sore throat lasting three days; two weeks later, he noticed that he was feverish and began to complain of pain in calves of both legs, especially in the region of the tendo-achilles. This pain persisted and became very intense three weeks before admission. Lying in bed relieved this pain to some extent, but standing or letting the feet hang over the bed aggravated the pain. Three days before admission, he began to notice some pain in the left wrist. There was no redness or swelling of the extremities. Marked anorexia had been present for the past three months. About five months prior to admission, the patient had a toothache followed by swelling and spontaneous rupture through the left lower cheek forming a draining sinus that persisted.

Examination of his past showed that he had measles and mumps as a child. Malaria was present at the age of 14 years, and he recovered promptly under treatment. There was no recurrence. In 1928, he had a urethral discharge lasting two days. Syphilis was denied by name or symptoms. He was a moderate drinker, and since childhood had an unusual craving for salt.

Physical examination: The patient was poorly nourished, pale, apprehensive, and looked acutely ill. Pupils were equal, regular, and reacted to light and accommodation. No nystagmus. No conjunctival petechiae. Tongue coated; pharynx congested; tonsils enlarged and reddened. On the lower left cheek opposite the first molar was a draining apical abscess. Neck showed no rigidity. Lungs were essentially normal. Heart was not enlarged. No murmurs at apex or base. Sounds were regular and of good quality. Liver and spleen were not felt and no tenderness was elicited. There was marked bilateral gastrocnemius tenderness, more marked on the left. Dorsiflexion of both feet induced pain in the calf muscles. There was hyperreflexia in both upper and lower extremities. Babinski negative. No sensory disturbances. Some weakness of both lower extremities. There was no evidence of any cranial nerve involvement. Rectal examination was negative. Eyegrounds revealed mild vascular sclerosis, but no nodules, aneurysms, or dilatation.

Laboratory studies: Repeated urine analyses revealed traces of albumin, red blood cells, white blood cells, and hyaline and granular casts. Specific gravity varied between 1.018 and 1.022. Phenolsulphonephthalein 65 per cent in two hours.

Blood chemistry, *April 30:* Sugar, 95.2 mg. per 100 c.c., urea nitrogen 14.8 mg. per 100 c.c. *May 27:* Sugar 88.9 mg. per 100 c.c., urea nitrogen 10.9 mg. per 100 c.c. *June 7* (four days before death): Sugar 117.6 mg. per 100 c.c., urea nitrogen 45.4 mg. per 100 c.c., creatinine 3.3 mg. per 100 c.c.; blood chlorides 465 mg. per 100 c.c.; cholesterol 124.3 mg. per 100 c.c.; urea clearance 117.9 per cent (May 14).

Blood Wassermann test negative. Gonococcus complement fixation test negative. Spinal fluid pressure 10 mm. Hg, clear, 8 cells. Wassermann test negative. Colloidal gold 0000000000. Stools persistently negative for ova, blood, and parasites. Stools, urine, and sputum negative for tubercle bacilli. Blood counts:

	May 1	May 7	May 11	May 25	June 2
White blood cells	14,200	19,200	28,800	23,200	22,400
Red blood cells, millions	3,68		3,18	2,9	2,6
Hemoglobin, per cent	75		62	48	40
Polymorphonuclear neutrophiles	79	76	85	78	89
Monocytes	3	11	1	1	2
Lymphocytes	18	4	10	15	8
Eosinophiles	0	7	4	6	1
Basophiles	0	2	0	0	0

Sedimentation time (18 mm.):

Date	Apr. 30	May 11	May 12	May 13	May 14	May 15
Time (in minutes)	8	15	15	12	12	8
Date	May 21	May 31	June 1	June 3	June 8	
Time (in minutes)	9	12	10	6	19	

Mantoux test, 1/1000 mg., negative. Culture from discharging sinus on face showed *Staphylococcus albus.*

Electrocardiograms: *April 30:* $T_{1, 2}$ depressed; T_3 isoelectric; T_4 diphasic. *May 13:* T_3 depressed; T_4 diphasic. *May 24:* $QRS_{1, 3}$ slurred. $T_{1, 3}$ depressed; T_4 diphasic. *June 5:* P_3 notched. $QRS_{1, 2, 3}$ slurred. T_1 isoelectric; $T_{2, 3}$ inverted; T_4 diphasic.

Roentgen-ray of chest, wrist, thigh, feet, forearm, legs, abdomen was essentially negative. Radiographic examination of the teeth revealed chronic apical abscesses of the first and second lower left molars.

Clinical course: The temperature fluctuated between 100° and 104° until the last week of life when it varied between 96° and 99°. The pulse remained proportional to the temperature elevation until the last week of life when it became relatively very rapid. Similarly, the respirations ranged between 20 and 28 until the last week when they varied between 48 and 60. The blood pressure varied between 118 and 130 systolic and 70 and 100 diastolic throughout the whole course. On May 5, a systolic pulmonic murmur appeared and this persisted until the very end. On May 9 (about 11 days after admission) several pin-head to pea-sized nodules were felt on the dorsum of the left forearm, and the posterior surface of the left leg. They were not tender. These nodules became progressively more numerous and larger, later appearing in the right supraclavicular area, and later felt along the course of the larger vessels of all four extremities. Three days after their appearance, biopsy of some of these nodules was performed and showed the following:

The specimen is that of subcutaneous tissue and accessory skin structures. The arteries show extensive infiltration of their walls with numerous polynuclears and round cells as well as occasional eosinophiles. The inflammatory cells extend through the adventitia into the subcutaneous fat. The intimal lining is proliferative and in a few areas the medial coat shows necrosis. Some of the arterioles are filled with thrombi.

Although the infiltration involves all layers of some of the vessels, giving the lesion the appearance of a panarteritis with complicating arteriole thrombosis, the characteristic medial necrosis of so-called panarteritis nodosa can be demonstrated in only a few of the vessels. Although the entire picture is highly suggestive of panarteritis nodosa, one cannot make this diagnosis with certainty from a study of this specimen.

Impression: Thrombo-arteritis (probably panarteritis nodosa). Thus the pathological report confirmed our clinical diagnosis.

On May 20, the patient complained of tingling in the finger tips of the left hand, followed on the next day by numbness of the right foot and numbness of the first three fingers of the right hand. Examination at this time revealed atrophy and weakness of both lower extremities, edema of the feet, diminished tactile sensation of the feet, and right foot drop. On June 4 (one week before death) he complained of numbness of the middle three fingers of the right hand and index finger of the left. There was poor coöperation, the patient was inattentive and appeared exhausted. Horizontal nystagmus appeared for the first time. The reflexes showed a hyperreflexia of the upper and lower extremities. Babinski negative. Abdominal reflexes were diminished. There was diffuse symmetrical muscle wasting and atrophy, greater on the right. There was marked wasting of the muscles of the lower extremities. There was lack of concentration, but sensation seemed grossly intact except in both

feet in which there was loss of position sense, marked diminution in tactile sensibility, and diminution of pain sense.

On June 2, the patient suddenly became dyspneic, respirations became very rapid with dilatation of alae nasi. Heart was rapid with a gallop rhythm. Many fine moist râles were present at bases of both lungs. The liver was large, four fingers below the costal margin, and there was marked pretibial and sacral edema.

These symptoms and findings persisted until death occurred on June 11.

Necropsy, Case 4. General: The body is that of a well-developed and well-nourished negroid adult male. There is a wound of a recent skin biopsy on the right forearm (figure 4).

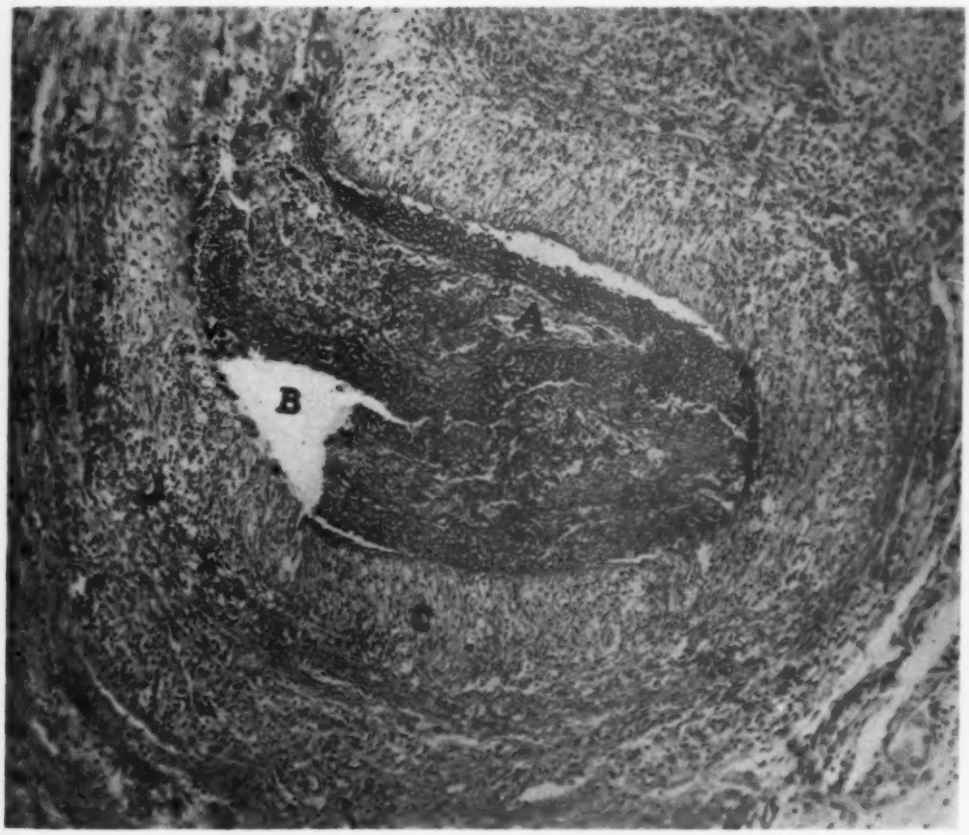

FIG. 4. Biopsy section of the subcutaneous nodule of the right forearm showing a platelet thrombus (*A*) occupying the lumen (*B*) of an artery, the wall of which (*C*) shows characteristic panarteritis. Many of the infiltrating leukocytes are eosinophiles. (170 ×.)

Cavities: Peritoneum contains 300 c.c. of clear yellow fluid. The entire right side is occupied by liver. Pleural cavities are filled with serous fluid. Pericardial cavity contains an increased amount of fluid.

Cardiovascular system: Heart weighs 360 gm. The chambers are dilated and the apex is rounded. Myocardium shows cloudy swelling and recent platelet thrombosis between pectinate muscles of left ventricle. Aorta shows patchy atheroma.

Respiratory system: Bronchi are filled with froth. Lungs show lobular pneumonia and chronic passive congestion.

Gastrointestinal system: Ileum (distal segment) contains a large amount of dark blood. Appendix (especially the submucosa) presents vascular changes characteristic of the acute phase of periarteritis nodosa with the usual medial necrosis.

Spleen weighs 75 gm. and is fibrotic. Two accessory splenules are present, one of which is embedded in the tail of the pancreas.

Pancreas weighs 135 gm., shows considerable fibrosis and obliterative intimal proliferation of arterioles. The tail contains an accessory splenule.

Biliary system: Liver weighs 1710 gm. After being severed from its attachment the organ shrinks to approximately half of its original volume. It is mottled deep red and yellow (figure 5). The red areas are suggestive of hemorrhagic in-

FIG. 5. Cut surface of the liver of case 4, showing distinct mottling (red and yellow), some of the areas suggesting infarcts.

farcts and are found mainly in the vicinity of portal channels in which the hepatic arteries present all stages of healed panarteritis, ranging from intimal thickening to almost complete fibrous obliteration of lumina. Some vessels also show aneurysmal dilatations.

Gall-bladder wall, especially the serosal layer, shows marked fibrosis and healed vascular lesions similar to those described in the liver.

Urinary system: The left kidney weighs 160 gm. and the right 180 gm. The capsule of each strips with difficulty leaving yellow-gray areas of fresh and old infarcts. Thrombi of various sizes fill lumina of arteries, some of which present aneurysms (figure 6). These vessels reveal all stages of acute, subacute and chronic panarteritis (figure 7). Fibrosis extends from arteries to surrounding framework. The tubules are filled with hyaline casts. Only occasional glomeruli show fibrosis. Ureteral walls are thickened to 3 mm. at their vesical orifices. Bladder is normal.

Genital system: Prostate is enlarged and shows subacute and healed stages of panarteritis. Testes show areas of fibrosis secondary to healed vascular lesions of panarteritis. Vas deferens shows recent and old panarteritic lesions.

Endocrine system: Adrenals weigh 14 gm. Peri-adrenal fat shows vessels with acute panarteritis.

Central nervous system: Brain shows numerous pontine vessels which are filled with red cell thrombi. Spinal cord shows hemorrhagic extravasations in the anterior horns involving many neurons.

Skeletal system: Quadriceps femoris muscle shows perivascular plasma and round cell infiltrations. Tendon of Achilles shows obliterative, intimal proliferation of arterioles.

Anatomical diagnosis: (1) panarteritis nodosa (acute and healed); (2) lobular pneumonia (terminal); (3) cardiac hypertrophy and dilatation; (4) mural thrombosis of left ventricle (terminal); (5) chronic passive congestion of viscera; (6) multiple serous effusions; (7) intestinal hemorrhage; (8) accessory splenules, multiple.

FIG. 6. Cut surface of the kidney of case 5. Small arrow points to thrombi occluding branches of the renal artery and hemorrhagic infarcts. The large arrow points to an aneurysm in one of these arteries.

Summary, Case 4: Young adult had sore throat three and a half months before admission followed in two weeks by pain in both legs and left wrist.

Examination revealed marked tenderness in both calf muscles with some weakness in the extremities. During his stay of six weeks in the hospital, he had fever (100° to 104°) until one week before death when temperature became subnormal; nodules appeared on all four extremities, and in the right supraclavicular area; sensory changes appeared in both hands and feet, and finally bilateral foot drop and muscle atrophy.

Laboratory examination: The blood pressure was normal. The urine always contained albumin, numerous red blood cells, hyaline and granular casts. The blood chemistry remained normal until four days before death when there was a definite elevation of urea nitrogen (45.4 mg. per cent) and creatinine (3.3 mg. per cent). Blood examination revealed a progressive anemia, hemoglobin decreasing from 75 per cent on admission to 40 per cent; red blood cells from 3,680,000 to 2,600,000; white

blood cells varied between 14,200 and 28,800; polymorphonuclear neutrophiles 76 to 89 per cent; eosinophiles 1 to 7 per cent. Sedimentation time was constantly increased. The electrocardiograms always showed definite evidence of ventricular myocardial damage.

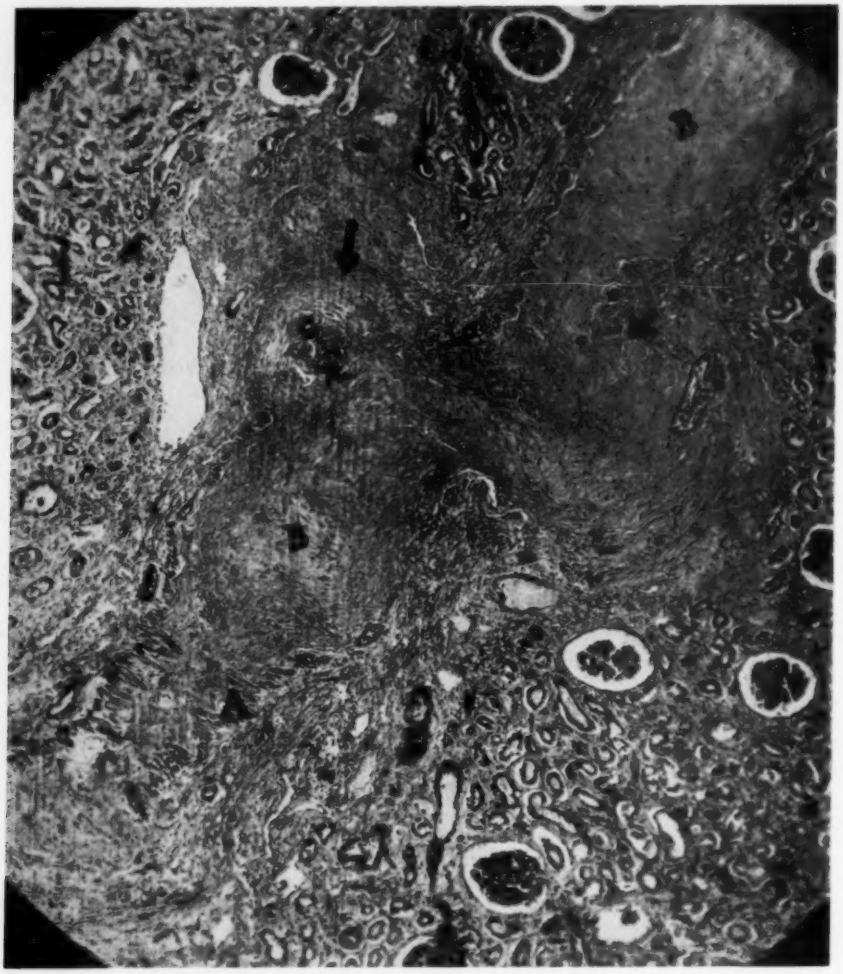

FIG. 7. Representative section through an artery of the cortex of the kidney of case 4 characterizing the healed stage of the obliterative arteritic lesion. Note fraying and marked thinning (large arrow) of the medial coat (*A*) at sites of aneurysm. One of these aneurysms is occupied by a giant cell (small arrow) granulomatous process (*C*). The rest of the lumen is completely replaced by hyalinized fibrous tissue (*B*) which also produces nodular thickening of the vessel wall. (100 ×.)

Autopsy revealed changes of panarteritis involving the appendix, liver, gallbladder, kidney, prostate, testicles.

Case 5. A. K., 35 year-old cook, was admitted May 21, 1937, died June 15, 1937.

Chief complaint on admission was generalized weakness of seven months' duration. She was in excellent health until seven months before. At that time she first noticed

weakness and became tired doing her work. These symptoms increased in intensity so that she was compelled to resign from her position. At this time, a cough developed associated with a slight amount of expectoration, and it persisted to the time of admission. She noticed that she began to lose weight and had drenching night sweats. Three months before admission, chills, occurring every third day and followed by drenching sweats, developed and continued until the present time. Accompanying these were frequency and urgency of urination and pain in the left lumbar region and groin. In addition, she had trouble with her eyes (photophobia, lacrimation, redness). During the entire course of her illness she had occasional abdominal cramps accompanied by vomiting. She became very irritable, crying at the slightest provocation. There was considerable epigastric burning about an hour after meals. About one month prior to admission, she noticed aching, weakness, numbness, and tingling of both arms and legs. There were frequent, severe headaches. She began losing her hair and observed that her hair was turning gray. These symptoms increased in severity so that in March 1937 she was removed to a hospital where she remained for one month, but no definite diagnosis was made and as she continued to become weaker, she went home. In her previous history there was a story of jaundice as a child in Finland. At the age of 19, she was told she had a gastric ulcer. At the age of 33 she was treated for "neuritis" of the right arm. She denied venereal disease. Was married for 12 years but never pregnant.

Physical examination: Adult white female, fairly well-nourished, pale, slightly puffy, looked acutely ill. There was definite evidence of loss of weight. There was severe muscle tenderness scattered over the entire body. Pupils reacted to light and accommodation, the left pupil was slightly irregular. No ocular palsies. Lid and bulbar conjunctiva injected. There was some circumcorneal injection. The right disc was blurred, the arteries narrowed, the veins engorged, and the macular region reddish. The left disc outline was clearer, the arteries narrowed, and the veins engorged. On the temporal side, about a disc distance from the disc, was a white area surrounded by pigment. No nodules were seen on the vessels. Ears and nose were negative. Teeth were in good condition, tongue clear and moist, pharynx injected. There were no palpable glands in the neck. The point of maximal impulse was in the fifth left intercostal space within the midclavicular line. There was regular sinus rhythm. Sounds were of good quality. There were no murmurs at the apex or base. The second aortic sound was equal to the second pulmonic. The lungs were clear. Liver and spleen were not felt. There was a bilateral foot and wrist drop with extreme tenderness over these extremities, especially on the right. Neurological examination: There was the peripheral type of long-stocking and long-glove sensory involvement. The deep reflexes were normal. The Babinski reflex was negative. There was some impairment of motor power with considerable pain and tenderness present. On finger-to-nose test, there was definite incoördination. Pelvic and rectal examinations were negative.

Laboratory studies: Blood Wassermann test negative. Spinal fluid Wassermann test negative. Fluid was clear, 60 cells, chiefly lymphocytes. Colloidal gold 1111000000. Blood culture sterile.

Blood chemistry: sugar 114.2 mg. per 100 c.c., urea nitrogen 12.5 mg. per 100 c.c., cholesterol 142.8 mg. per 100 c.c., calcium 9.3 mg. per 100 c.c., phosphorus 4.8 mg. per 100 c.c., chlorides 510 mg. per 100 c.c., icterus index 5. Van den Bergh negative direct and indirect. Agglutination for typhoid, paratyphoid A and B, *B. melitensis* and *abortus* was negative.

Urine examination showed specific gravity varied from 1.010 to 1.020. Repeated specimens showed 1 to 2 plus albumin, many red blood cells, and granular casts. Phenolsulphonephthalein excretion was 15 per cent in two hours, 40 per cent in four hours. Urea clearance was 49.7 per cent. Urine was negative for arsenic and lead.

Roentgen-rays of skull, left upper and right lower extremities, and lumbar and lower dorsal spine were negative.

Roentgen-ray of chest showed no pulmonary infiltration in the upper part of the chest. The left diaphragmatic leaf was dimly visualized, disappearing within a hazy, veil-like opacity which obscured the diaphragmatic leaf as well as the left costophrenic sinus. The following possibilities should be considered: "fluid in the left costodiaphragmatic recess, splenic infarct with a reaction on the pulmonary side of the diaphragmatic leaf. In view of the absence of consolidation anywhere in the chest, it is highly improbable that we have to deal with pleuro-pulmonary pathology."

Blood counts:

	May 21	May 25	May 28	June 2	June 15
White blood cells	14,400	14,300	12,800	9,100	6,000
Red blood cells, millions	3,6	3,68		3,46	2,94
Hemoglobin, per cent	60	68		54	40
Polynuclear neutrophiles	76	82	73	69	54
Monocytes	5	2	4	4	2
Lymphocytes	16	14	21	22	44
Basophiles	0	0	0	1	0
Eosinophiles	2	2	2	4	0

Bleeding time 1½ minutes, coagulation time 8 minutes, fragility test .54 to .36 per cent, blood platelets 390,000.

Sedimentation time: (18 mm.) May 23, 30 minutes; May 28, 18 minutes; June 1, 23 minutes.

Electrocardiograms: *May 25.* Regular sinus rhythm, rate 140. $QRS_{1,3}$ slurred; QRS_3 diphasic. $T_{1,2}$ depressed; T_3 isoelectric. *May 27.* Regular sinus rhythm, rate 130. $QRS_{1,2,3}$ slurred, QRS_3 diphasic. $T_{1,2}$ depressed, T_3 isoelectric.

Clinical course: The temperature on admission was 101.2° and fluctuated between 101° and 104° throughout the stay in the hospital with the exception of a sudden drop on the morning of the sixth day to 98.6° and a sudden elevation on the day of death to 107°. The pulse was more rapid than the temperature warranted. The blood pressure varied between 90 and 145 systolic, and 30 and 84 diastolic. On the third day, the patient developed a gallop rhythm which persisted for five days. On May 26 she experienced fits of extreme depression alternating with fits of crying. This persisted for several days. Three days after admission, a few pin-head-sized nodules were felt in the popliteal fossae, and later additional ones were palpated along the large vessels of the forearms. Two weeks after admission, the liver became palpable two fingers below the costal margin. One week before death there was complete loss of position and tactile sense in her lower extremities. There was ankle and pretibial edema. Three days before death she became extremely cyanotic, was euphoric, incoherent, and exhibited echolalia. The abdomen was markedly distended. The liver was three fingers' breadth below the costal margin, whereas the spleen could not be felt. The face was puffy. On the day of death, the temperature rose to 107°, the heart sounds were very rapid and distant, and there were fine twitchings of the muscles of the face. The pain in the legs was excruciating, and tenderness on pressure remained constant throughout the course of her stay at the hospital. She died on June 15 from cardiac failure.

Necropsy, Case 5. General: The body is that of a well-developed and moderately under-nourished white female. There is a biopsy scar over the right deltoid region.

Cavities: The right pleural space contains old, and the left, recent adhesions. The visceral and parietal pericardial linings are adherent and show acute fibrinous inflammation. The mediastinum contains a dense mass, 4 by 3 by 2 cm., situated between the aorta and left main bronchus (figure 8). The mass is firmly adherent to both structures, follows along the aorta, and on section presents a firm gray and

yellow appearance. Microscopically, it is a granulomatous mass which contains areas of necrosis, fibroblastic proliferation, few multinucleated giant cells, suggestive epithelioid cells, hyalinization of fibrous tissue and perineural infiltration (figure 9).

Cardiovascular system: Heart weighs 500 gm. Myocardium is flabby and shows cloudy swelling. Aorta shows patchy atheroma.

Respiratory system: The medial border of the upper lobe of the left lung is in anatomical continuity with the mediastinal mass, the lung parenchyma showing caseous

FIG. 8. Heart and mediastinal mass between left bronchus and aorta, of case 5. The aorta is almost entirely encircled by the granulomatous mass. The trachea and bronchi are here shown displaced in order to bring the relationship of the mass into better view.

necrosis as well as epithelioid and giant cell reaction (figure 10). The left lower lobe anteriorly shows thrombosis and infarction with superimposed suppuration. Other areas show fibrous replacement and calcification of parenchyma, chronic passive congestion, and lobular pneumonia. Blood vessels show proliferative vascularized subintimal connective tissue with narrowing of the lumena and infiltrative changes in the media and adventitia.

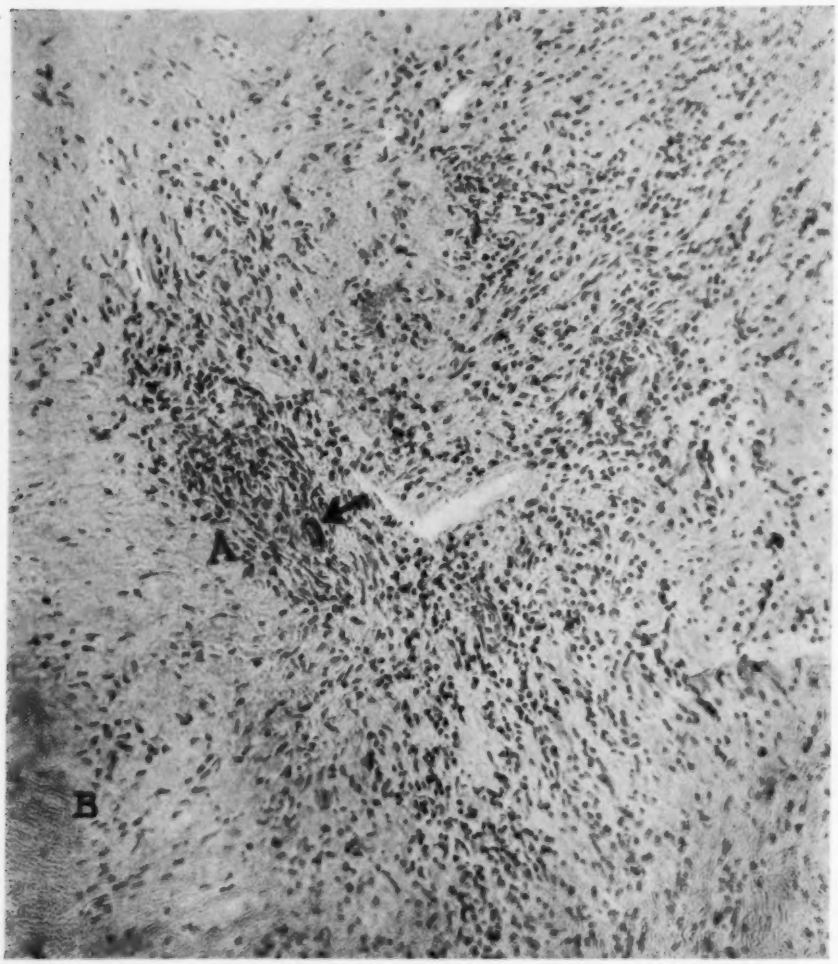

FIG. 9. This is a section through a representative portion of the mediastinal mass of case 5. Note the marked fibroblastic reaction and hyalinization (*A*), the areas of necrosis (*B*), and multinucleated giant cells (arrow) surrounded by groups of elongated epithelioid cells. (210 ×.)

Gastrointestinal system: Esophageal wall presents an occasional small artery which is the seat of perivascular infiltration. Vermiform appendix presents a characteristic argentaffinoma.

Spleen weighs 210 gm. and shows marked perisplenitis. The parenchyma reveals infarction, suppuration, tubercle-like lesions with giant cells resembling tuberculosis,

and necrotizing central arteriolitis. Some of the central arterioles show giant cells and granulomatous changes in the intima (figure 11).

Pancreas weighs 135 gm. The vascular changes consist of granulomatous thrombo-arteritis with giant cells and epithelioid cells, the lesions being those of acute and healed panarteritis. One vessel shows a "tubercle-like" structure in the wall.

FIG. 10. Section of lung of case 5, taken through the medial border of the left upper lobe, where the latter merges with the mediastinal mass. Note the caseous necrosis (*A*) with a peripheral zone of Langhans giant cells (*B*) directly continuous with the granulomatous structure (*C*). The latter, in turn, is in anatomical continuity with atelectatic lung and bronchioles (*D*). (130 ×.)

Biliary system: Liver weighs 2280 gm. and shows marked congestion and focal hemorrhagic necrosis.

Gall-bladder wall shows healed and granulomatous vascular lesions. The lumen of the viscus and its duct contain small calculi.

Urinary system: Kidneys weigh 230 gm. each and show subacute nephritis with

atypical crescents, interstitial edema and leukocytic infiltration. Tubules contain blood and polynuclear cells. In areas the stroma contains epithelioid and giant cells. Some of the arcuate arteries are thrombosed with only an occasional infarct. Ureters and bladder are normal.

Genital system: Uterus shows vascular changes of granulomatous thromboarteritis similar to those observed in the other organs.

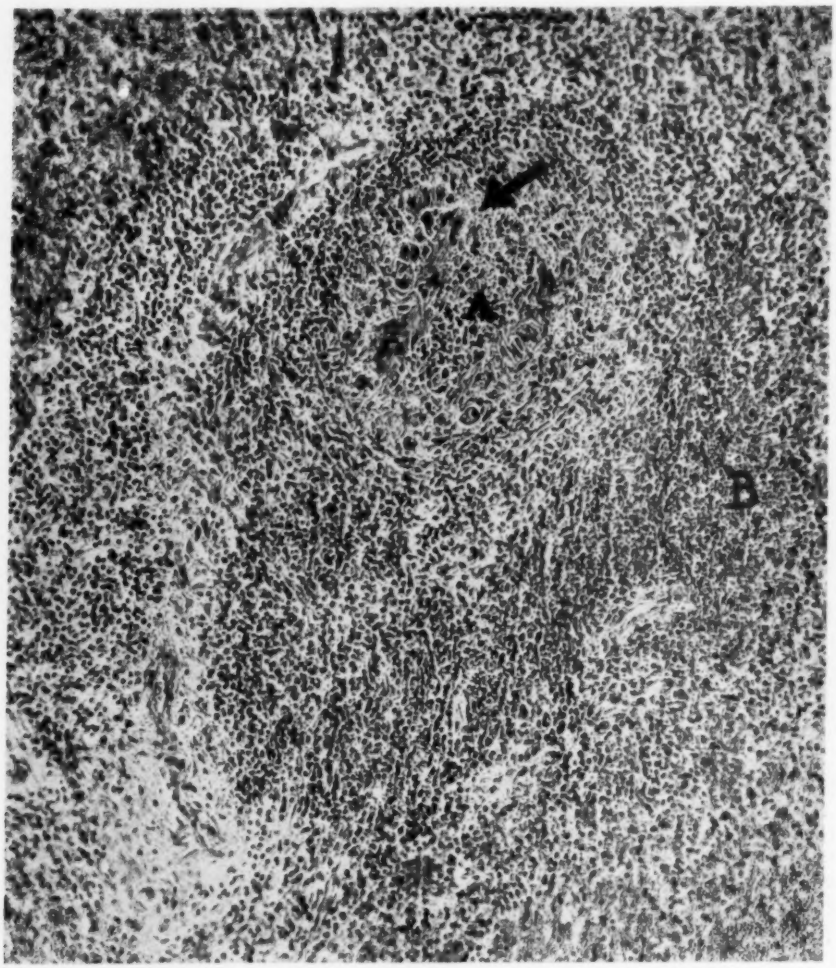

FIG. 11. Section of spleen of case 5, through a corpuscle showing Langhan's giant cells (arrow) replacing its germinal center. Also, note incipient acute inflammatory infiltrate (*A*) which becomes much more marked in the pulp (*B*) and which also assumes a suppurative character in other portions of the spleen. (200 ×.)

Lymphatic system: Mediastinal lymph nodes are involved in the mass described under mediastinum, and show the same histopathologic changes found in the mass.

Endocrine system: Adrenals show tubercle-like lesions in the capsules and marked vascular changes consisting of acute and granulomatous panarteritis with thrombosis. The vessel walls contain epithelioid and giant cells, and areas of necrosis of the media,

although the latter is not as extensive as usually seen in the acute phase of periarteritis nodosa (figure 12).

Skeletal system: Sections of diaphragm and pectoralis muscle show healed panarteritis. The pectoralis muscle also contains encysted trichinae.

Central nervous system: Brain shows congestion and edema.

Bacteriology: Stains of the sections and direct smears of organs are negative for tubercle and leprosy bacilli as well as for spirochetes.

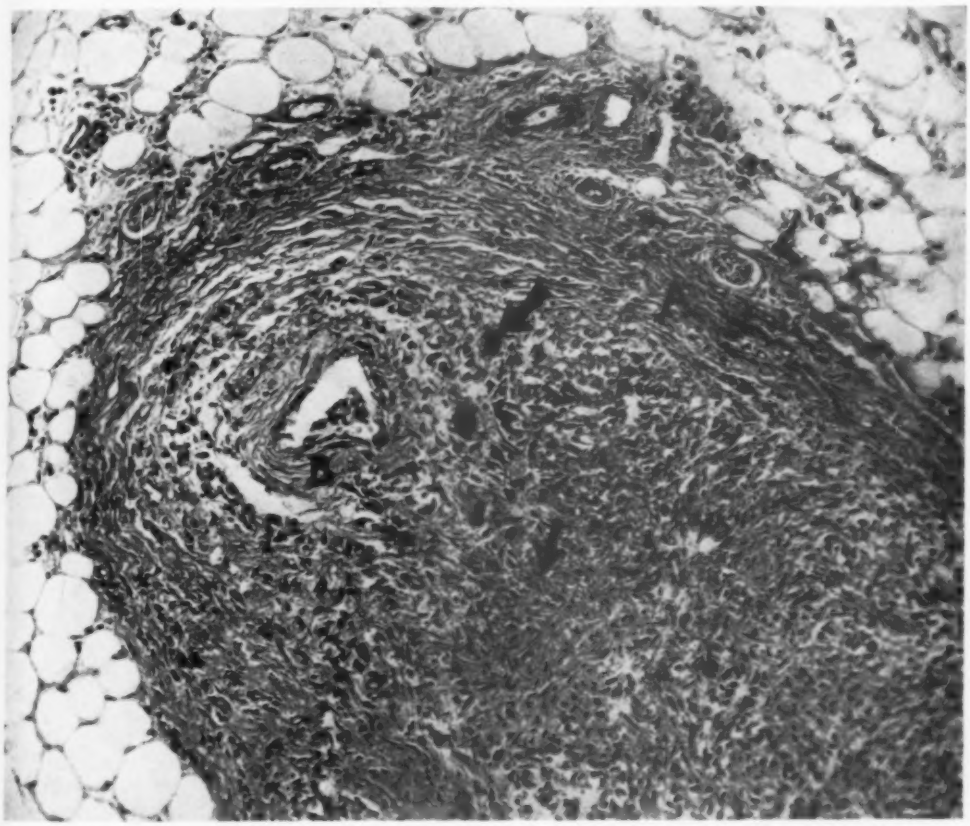

FIG. 12. Section of periadrenal tissue of case 5 showing granulomatous structure and giant cells (arrows) replacing the lumen and wall (*A*) of a small periadrenal artery. Note attempt at recanalization (*B*) of the occluded lumen. (200 ×.)

Anatomical diagnosis: (1) Panarteritis, granulomatous (etiology undetermined); (2) granuloma of mediastinum and lung; (3) multiple visceral infarcts; (4) subacute glomerulonephritis; (5) lobular pneumonia (terminal); (6) cardiac hypertrophy and dilatation; (7) chronic passive congestion of viscera; (8) argentaffinoma of appendix; (9) chronic cholecytitis and cholelithiasis; (10) trichiniasis (encysted); (11) deltoid scar (biopsy).

Summary, Case 5. Adult female, 35 years of age, was admitted with complaints beginning seven months before admission consisting of weakness followed by cough, loss of weight, night sweats, chills, frequency and urgency of urination, eye signs (photophobia, lacrimation, redness), recurrent abdominal cramps, extreme irritabil-

ity, aching, weakness, numbness and tingling of both arms and legs, frequent severe headaches, hair turning gray with some loss of hair.

Repeated examinations revealed a fairly well-nourished and pale female, progressively losing weight. The heart exhibited a gallop rhythm and gradually grew weaker. There were psychotic changes. A few nodules were palpable in the popliteal fossae and along the large vessels of the forearms. The abdomen was markedly distended, and the liver was enlarged. There was ankle and pretibial edema. There was severe muscle tenderness all over the body, most intense over the lower extremities. There was bilateral foot and wrist drop with peripheral type of long-stocking and long-glove sensory involvement. Fever, leukocytosis, anemia, and increased sedimentation rate were present. Repeated urine examinations showed albumin, casts, and red blood cells.

Autopsy revealed the following: A granulomatous lesion in the mediastinum and left lung. Changes characteristic of panarteritis nodosa in the lungs, spleen, pancreas, liver, gall-bladder, kidneys, uterus, adrenals, diaphragm, and pectoral muscles. Encysted trichinae in the pectoralis muscle.

Clinical Symptoms and Signs in Cases Reported: Cases included three males and two females. The age of the patients varied from 25 to 49 years. This series showed an average duration of five months from the onset of symptoms to death.

Summary of Symptoms and Signs in Five Cases of Periarteritis Nodosa:

Fever	4	Abdominal pain	3	Dyspnea	2
Albuminuria	4	Pain in extremities	3	Subcutaneous nodules	2
Hematuria	4	Foot drop	3	Purpura	2
Edema	4	Loss of weight	3	Headache	1
Hepatomegaly	4	Tingling sensation in extremities	2	Pain in chest	1
Leukocytosis	3	Visual disturbances	2	Atrophy	1
Eosinophilia	3	Cough	2	Cyanosis	1
Chills	3	Vomiting	2	Icterus	1
Weakness	3	Sweats	2	Splenomegaly	1
Hypertension	3			Positive Wassermann	0

General Discussion on the Pathological Findings of This Series of Cases

The numerous and varied pathological changes observed in these cases compare favorably with the findings of previous observers. It seems advisable to note, although at the risk of repetition, that the findings described above have, as a common underlying process, an arteritis. This arteritis is found in acute, subacute or chronic phase. Frequently two, or all three stages are demonstrable in the organs of the same case, even in the same organ. Equally frequent in occurrence are the findings representing the various complications of arteritis which one would logically expect to encounter. They are (1) necrosis of vessel wall with hemorrhage, recent or old; (2) thrombosis of arteries with hemorrhagic or anemic infarctions, recent and old; (3) aneurysmal dilatation of arterial walls with secondary changes, such as hemorrhage, due to rupture, pressure necrosis of surrounding tissue; and, finally, (4) replacement fibrosis of thrombi as well as of the tissues destroyed by the above described secondary changes. The reparative process of recanalization of thrombi, although described frequently, is not a prominent feature of the later changes observed in this series of cases.

A little more detailed analysis of our findings reveals several additional features worthy of note, the most interesting one of which is provided by case 5. In this case, the mediastinal granuloma and the giant cell reaction are intriguing findings. The gross character produced by the dense fibrosis in the mediastinal mass, the caseous necrosis and giant cell reaction in the lung, the miliary abscesses and giant cell reaction in the spleen have led noted pathologists who were shown the specimens to suggest a number of possible etiological agents among which may be mentioned syphilis, tuberculosis and Hodgkin's disease. One keen clinician even suggested the possibility of leprosy. However, to date none of these suggestions could be confirmed. Parasitic etiology was considered early in the study of the case as a possible explanation for the granulomatous changes in the lesions but with unsuccessful attempts at proof, although, strangely enough, encysted trichinae were found in the pectoralis muscle. However, the relative frequency of occurrence of this lesion to which the recent literature calls attention, adds little support to trichiniasis being the causative agent in this particular case.

In discussing the etiology of this disease, the above-described cases provide much food for thought. One cannot refrain from considering the etiology of this disease to be almost as protean in nature as are the varied anatomical changes. In addition to a possible underlying syphilis, Hodgkin's disease, tuberculosis, leprosy and parasitic infestation, mentioned in the study of case 5, one may consider the intense polymorphonuclear cell reaction and occasional suppuration as evidence of a non-specific pyogenic agent, whereas the abundance of eosinophiles may be considered an expression of allergy, rather than that of a parasitic infestation. With the exceptional granulomatous changes observed in case 5, as well as the varied findings observed in the other cases in this series, it is obviously very difficult to determine any pathognomonic histopathologic changes which might point to the causal agent in any given case. It is very likely that the secondary and complicating or coincidental changes (unrelated to the disease) so disguise the picture as to make the recognition of a specific histopathology of a "pure" case of this disease well nigh impossible. Many of the unexplained fibrosed or recanalized blood vessels which, in the past, have been encountered in routine postmortem examinations and biopsies and which have been previously brushed aside for want of explanation, may have been healed lesions of panarteritis of varying degree (caused by various agents) which had existed as localized lesions or unrecognized during life.

It is also worthy of note that varying degrees of cirrhosis of the liver were present in all cases of this series. The process most likely represents healed lesions of panarteritis. Although acute changes were not demonstrable in all of the cases, the scarring, which contributed to the cirrhosis and which most probably represents old healed lesions, was a constant finding.

The lobular pneumonia which was found in most of the cases appears to be a terminal event and without any special significance.

The presence of hyperplastic splenic tissue (accessory splenules and splenomegaly) also seems unrelated to the disease.

Finally, it may be mentioned that this series of cases afforded the rare opportunity to study the changes in the central nervous system. The thrombus in the left internal carotid artery and the changes which it produced in the left frontal lobe of case 1 are of special interest in this regard. The somewhat similar findings in the smaller vessels of the pons in case 4, as well as the multiple hemorrhages observed in the spinal cord, lead one to conclude that the central nervous system is not spared in this disease.

Diagnosis

Many authors have attempted to present a symptom complex as diagnostic of the disease, varying from the triad of symptoms, "chlorotic marasmus," polymyositis and polyneuritis, and gastrointestinal symptoms to a sextet of symptoms: gastrointestinal, renal, neuromuscular, cardiac, cerebral, and cutaneous, to the unstated number of symptoms based on vascular disturbances in the particular organs or regions affected. Thus, the complexity of the clinical picture is apparent. The diagnosis of periarteritis nodosa is to be considered in any continued illness, and while the symptoms may be related to all the organs involved, no symptoms of the disease may be present as in our case 2.

In the 106 cases reported in the English literature a correct antemortem diagnosis was made in 30, including four of our five cases. In some instances, the diagnosis may be verified by biopsy of a subcutaneous nodule or muscle, examination of a surgical specimen, or laparotomy.

Prognosis and Treatment

Harris, Lynch, and O'Hare [3] in reviewing the 101 cases reported in the English literature state that nine of those patients may be alive and five are definitely known to be alive. A patient may survive periarteritis nodosa if the disease remains localized in some organ such as the appendix or, if in a vital organ, progresses to the healed stage without producing functional insufficiency. All our cases died. There has been no specific treatment that has had any success at the present time. Symptomatic therapy should be used.

Summary

Five cases of periarteritis nodosa are reported four of which were diagnosed ante mortem.

The clinical picture and autopsy findings are presented in all five cases.

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THE CLINICAL VALUE OF STERNAL BONE MARROW PUNCTURE *

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IN the past decade the introduction and widespread application of sternal aspiration for the study of the living bone marrow have given the clinician a simple and practical method of studying hemopoiesis during life. This method of examining bone marrow has come into favor because of the ease of securing material and the great value of the information obtained. Bone marrow biopsy, although preferable to the simple aspiration method because the marrow architecture is preserved, is a surgical procedure requiring an operating room set-up and several days for the preparation of the material. Sternal puncture, on the other hand, is a simple bed-side procedure, easily tolerated by the patient, and in most instances it yields sufficient information for diagnosis. Occasionally repeated punctures may be necessary in a given case before a correct diagnosis can be made, but as a rule no ill effects are caused patients by such repetitions. This ease of performance, the satisfactory material obtained, and the fact that the composition of the sternal marrow may be taken as representative of the whole mass of the hemopoietic tissue, make sternal puncture an acceptable method for studying living bone marrow in all its phases. Scott,[1] in his excellent monograph on the subject best summarizes its value when he states: "sternal marrow puncture provides an opportunity of hematologic education which has never previously existed, it is in Schulten's words: 'die Hochschule für den Haematologen.' "

Very little was known about the physiology of bone marrow until the time of Neumann's[2] investigations in 1868 when he showed that the marrow was the site of erythropoiesis. In the following year he[3] demonstrated that it was also the site of leukopoiesis. Before these investigations the bone marrow was regarded merely as a mechanical filler of the medullary cavities of bones. The studies of bone marrow changes during disease which followed Neumann's work were not satisfactory because the material was obtained at postmortem examinations and hence did not portray living hemopoiesis. The study of the human marrow during life was instituted in 1908 by Ghedini[4] who performed biopsies of the tibial marrow for the diagnosis of malaria. However, it was not until 1923 that Seyfarth[5] suggested trephining the sternum for the study of bone marrow. The technic used by him required a surgical set-up and accordingly did not come into common use until Arinkin's[6, 7] important works in 1927 and 1929. He was the first

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to "needle puncture" the outer plate of the sternum, aspirate marrow, make smears, and study living bone marrow. Since his reports there have been numerous other investigations which have corroborated the conclusions reached by him and which have reëmphasized the value and importance of sternal puncture. In the recent papers of Scott[1] and Vogel, Erf, and Rosenthal[8] the subject is completely reviewed.

Many workers have stressed the superiority of sternal trephine over aspiration. Our experience, however, indicates that the ease of performance and the sufficiency of information gained from sternal aspiration in most cases make it the method of choice as a routine procedure. If the desired information is not obtained by aspiration, trephine or biopsy can be performed. In only a few cases have we been unable to obtain marrow material for diagnosis by aspiration, so that we now limit the surgical procedure of trephining to cases from which no diagnostic marrow can be obtained by sternal puncture. This has occurred twice in 300 sternal aspirations: (1) A 67-year-old male who presented a leukemic peripheral blood picture (11,500 leukocytes with 27 per cent myelocytes) and who yielded a "dry" sternal puncture. Subsequent studies proved this to be a case of Albers-Schoenberg's disease with no normal marrow cavities. (2) A 48-year-old female whose "dry" sternal aspiration was owing to the presence of an aplastic anemia with dense sclerosis of the bone marrow. We feel, therefore, that only in instances in which aspiration yields no marrow or where insufficient information is obtained by aspiration is sternal biopsy indicated.

Sternal marrow puncture is indicated in all cases suggesting disorders of the blood forming organs or reticulo-endothelial system, or whenever the clinician seeks to follow hematopoiesis during life. It is indispensable in the diagnosis of blood dyscrasias, or when such a diagnosis must be excluded.

This report was prepared to analyze our experiences with sternal puncture during the past three years. Our purpose was three-fold: (1) to redetermine for ourselves and to check, if possible, the criteria of normal sternal marrow as laid down by other authors, particularly those which have appeared in the literature during the past few years; (2) to study the marrow of all cases showing or suspected of suffering from blood dyscrasias or disorders of the reticulo-endothelial system, and (3) finally to correlate, if possible, such marrow findings with the underlying disease process.

We have selected as our "normal" group patients entering the hospital with no evidences of blood dyscrasias or of disturbances of the reticulo-endothelial system. These patients were admitted for conditions which in no way affected hematopoiesis and were unassociated with bleeding or fever. Patients with functional disorders made up the bulk of this group, namely: cases of neuroses, hysteria, spastic neurogenic colon, cardiospasm, and cases admitted for observation which after complete investigation proved to be free of any organic ailment. Other "normals" included cases of uncomplicated diabetes mellitus, diabetes insipidus, uncomplicated hernias prior to operation, undescended testicle, visceroptosis, uncomplicated peptic ulcer, etc.

There were 115 cases in this "normal" group; their ages ranged between 15 and 50 years.

Method of Sternal Puncture. Jaffe[9] and others have shown that the larger the quantity of marrow material aspirated the greater is the dilution of this material with peripheral blood from the marrow venous sinuses. On the other hand, the smaller the quantity aspirated the greater is the concentration of marrow proper obtained for study. We have accordingly employed the method limiting the aspiration to 0.1 to 0.2 c.c. of marrow material. With the patient flat on his back, 0.5 c.c. of ½ per cent novocaine solution is injected intracutaneously and subcutaneously over the sternum in the midline just below the level of the second rib. After waiting one or two minutes for the anesthetic to take effect, an 18 gauge sternal puncture needle with a sharp short bevel (we used the regular Barker stainless steel spinal needle, cut down to the size of 1¾ inches for adults and to ½ to ¾ inch for infants and children) is inserted into the anesthetized area at right angles to the sternum. A rotary drilling motion is used to penetrate the outer plate of the sternum. As the needle enters the marrow cavity an abrupt and sudden "give" can be felt by the operator. The stylette is now removed and a tight 1 or 2 c.c. syringe is attached to the needle and between 0.1 and 0.2 c.c. of marrow is aspirated. The needle with the syringe attached is then quickly withdrawn and the puncture point sealed with a drop of collodion. The entire procedure requires approximately two or three minutes. The aspirated material is then expelled on a glass slide from which smears and counts are made. The smears can be easily differentiated macroscopically from peripheral blood by the presence of visible fat globules and microscopically by the presence of immature marrow cells. The stains used were Wright's and Jenner-Giemsa, allowing double the time required for the staining of peripheral blood smears.

For our first 100 cases we counted 500 cells for each differential. Later it was found that if the smears were evenly spread the same information could be obtained by counting 200 to 300 cells. Total counts were made on each examination, but in general it was found not to be so important as the differential count, additional confirmation of the principle that diagnoses in hematology depend more on the types of cells found than on their number. The range in the total counts among our "normal" subjects was great. We found in some "normal" marrows total counts as low as 15,000 nucleated cells and in others as high as 160,000 per cu. mm. In the cases of leukemia were found, as a rule, the highest number of nucleated cells, yet in some instances of leukemia the total counts fell within the accepted normal range.

The findings in the 115 "normal" cases are given in table 1.

It is well to point out again that these values in the main agree with those reported in recent publications on this subject. In hematology much confusion exists because investigators have applied different names to the same cells and also because of the tendency to individualize relatively minor differences of perhaps doubtful significance in cellular structure. We have

TABLE I

Leukopoietic Elements:	
Myeloblasts	1.2%
Promyelocytes	0.5
Myelocytes	7.0
Metamyelocytes	12.4
Non-segmented neutrophiles	21.5
Segmented neutrophiles	35.7
Basophiles	0.2
Eosinophiles	2.1
Eosinophilic myelocytes	0.6
Hematogones	3.3
Reticulum cells	1.1
Lymphocytes	13.5
Monocytes	0.7
Plasma cells	0.1
Megakaryocytes	0.1
Erythropoietic Elements:	
(per 100 white blood cell elements)	
Megaloblasts	1.0
Erythroblasts	5.3
Normoblasts	9.1
Ratio Leukopoiesis to Erythropoiesis:	
100 : 15.4	

attempted to use as simple a classification as possible, employing names familiar to most clinicians as well as to the hematologists and pathologists, and have avoided as far as possible unimportant subgroups of the same cell.

Many adequate descriptions of the marrow cells are available in textbooks and recent publications. Most of the primitive cells of the myeloid series occur normally in the bone marrow and should present no difficulty in diagnosis with proper staining. We have not attempted to differentiate between myeloblasts and lymphoblasts but have depended upon the associated cell type to settle this question in the particular case studied. The promyelocyte, myelocyte, and metamyelocyte are easily recognized. The neutrophilic granulocytes are divided into the non-segmented and segmented forms. The eosinophile and eosinophilic myelocyte, the basophile, plasma cell, monocyte, and lymphocyte offer no difficulties in differentiation to anyone already familiar with smears of normal peripheral blood. The reticulum cell, "hematogone," and the megakaryocyte are never found in the peripheral blood normally. The reticulum cell originates from the reticulo-endothelial system and is a large cell possessing a granular gray blue cytoplasm with serrated margins and an ovoid nucleus. The "hematogone" is smaller than the lymphocyte, has a dense solidly staining nucleus occupying nearly the entire cell and shows very little cytoplasm. The megakaryocyte (the progenitor of the platelet) is the largest cell encountered in bone marrow. It shows a finely granular bluish cytoplasm usually with multiple purplish nuclei. Often small bodies of platelets can be seen breaking off.

In the erythropoietic series we have differentiated three principal types of cells: (1) megaloblast, (2) erythroblast, and (3) normoblast. We have made no attempt further to divide these cells into sub-groups as some others have done. These cells are not seen in the normal peripheral blood, although

in hemorrhage or other irritative states of the marrow, normoblasts may be found peripherally. Early in our studies we did routine reticulocyte counts, but later abandoned this because it afforded no helpful information and because the findings indicated that erythropoiesis could be better determined by the increase in the immature erythropoietic cell groups than by the determination of the reticulocyte activity. There are those who do not believe that the megaloblast is ever seen in a normal bone marrow and that its presence indicates pathologic erythropoiesis seen only in pernicious anemia. We, however, are inclined to agree with those who regard it as the youngest evidence of normal erythropoiesis and have, therefore, included it in our figures of normal bone marrow.

We have found useful, as have others, the ratio of leukopoiesis to erythropoiesis. In this work the normal ratio was 100: 15.4. Variations from this normal ratio were found significant, as will be shown throughout this work.

Primary Pernicious Anemia: We have studied 12 cases of primary pernicious anemia. Seven were studied in the stage of relapse. These showed peripheral counts ranging between 30 and 40 per cent hemoglobin (Sahli)* and 1,300,000 to 1,800,000 red blood cells with reticulocyte counts ranging between 0.5 and 0.9 per cent. In all of these cases the bone marrow before liver therapy was begun was definitely megaloblastic. The cellularity was increased, the increase being chiefly of the immature erythropoietic elements. The ratio of leukopoietic to erythropoietic elements changed from 100: 15 to 100: 94. Reticulocytes in the bone marrow in relapse were too few to be counted. These findings are shown in table 2.

TABLE II

Erythropoietic Elements: (per 100 white blood cell elements)	
Megaloblasts	10.9
Erythroblasts	28.9
Normoblasts	54.5

In some cases, as early as 24 hours and in others within 48 hours after institution of liver therapy, the bone marrow underwent a transition from the megaloblastic to the normoblastic phase. Five patients were studied by serial sternal punctures during the course of liver therapy. Their peripheral blood counts ranged from 46 to 60 per cent hemoglobin (Sahli) with 1,900,000 to 2,700,000 red blood cells per cu. mm., reticulocytes from 7 to 20 per cent. The beginning maturation and liberation into the blood stream of the erythropoietic elements of the marrow were shown by the following alteration in the leukopoietic: erythropoietic ratio from 100: 94, in state of relapse, to 100: 48 during treatment, and by the rapid maturation of the erythropoietic cells to more mature forms, shown in table 3.

* Throughout this work 14.5 gm. hemoglobin are equivalent to 100 per cent hemoglobin (Sahli).

TABLE III

Erythropoietic Elements: (per 100 white cell elements)	
Megaloblasts	3.0
Erythroblasts	18.1
Normoblasts	27.3

Six patients were studied during remission. Several sternal aspirations were made in each case. Peripheral blood counts on these patients had reached normal, ranging from 80 to 100 per cent hemoglobin (Sahli), with red blood cell counts ranging from 4,000,000 to 5,000,000 per cu. mm. and reticulocyte counts from 1.2 to 3.2 per cent. At this phase the marrow showed few or no immature erythropoietic elements. Erythropoiesis at this stage was normal as evidenced by the restoration of the normal ratio of leukopoiesis to erythropoiesis 100 : 18, as shown in table 4.

TABLE IV

Erythropoietic Elements: (per 100 white blood cell elements)	
Megaloblasts	1.2
Erythroblasts	4.6
Normoblasts	12.5

Changes in the leukopoietic elements of the bone marrow in active primary pernicious anemia are insignificant. Although peripheral counts show a slight decrease of the total white cells with a shift to the right, evidenced by hypersegmentation of the nuclei of the neutrophiles, very little significant change from the normal was found in bone marrow granulopoiesis in this study. Some have reported alterations in the megakaryocytes. This we were unable to confirm. The failure of maturation of the red blood cell elements in this type of anemia was well shown by the megaloblastic marrow in the patients in relapse, and by the transition from this stage to a normoblastic marrow as specific therapy was instituted. This change was best studied by serial sternal punctures which may reveal progress or failure in treatment more adequately and earlier than any other method.

Macrocytic or Hyperchromatic Anemia of Pregnancy. One such case was studied. This was a white female in her seventh month of gestation. Her peripheral blood count showed 38 per cent hemoglobin (Sahli), 1,500,000 red blood cells per cu. mm. and 0.9 per cent reticulocytes. Her course in the hospital differed in no way from that of patients with primary pernicious anemia. On liver therapy she showed a reticulocyte response of 22 per cent within five days, and within several weeks her peripheral count reached 80 per cent hemoglobin (Sahli) with 4,000,000 red blood cells per cu. mm. and a normal reticulocyte count. Her bone marrow before, during and after treatment resembled in all respects that seen in pernicious anemia in its corresponding phases.

Data concerning bone marrow findings in other hyperchromatic or macrocytic anemias are scanty. However, some observers, particularly Rohr

(cited by Scott [1]), report the findings in sprue to be indistinguishable from that of pernicious anemia.

Iron Deficiency Anemias. There were five patients with the idiopathic hypochromic achlorhydric variety of anemia. All were middle-aged women. In two cases there was a history of a slow blood loss over many years due to menorrhagia. In the others there was no history of blood loss. In the marrow leukopoiesis showed no significant deviations from the normal. However, the erythropoietic tissues showed a hyperplastic active marrow, the activity being proportional to the degree of anemia. There was an increase in normoblasts and erythroblasts during the anemic phase and a return to normal during treatment. One such patient with 40 per cent hemoglobin (Sahli) and 3,000,000 red blood cells per cu. mm. peripherally showed in her marrow before treatment the following: 1 megaloblast, 8 erythroblasts, and 18 normoblasts per 100 white blood cells counted, or a ratio of leukopoietic: erythropoietic elements of 100:27 instead of the average normal ratio of 100:15. As the anemia was corrected with iron therapy, the ratio as well as both the peripheral and bone marrow pictures returned to normal.

Anemia Due to Hemorrhage. In this group of cases the marrow changes apparently depended on the degree and the rapidity of the blood loss. In slow hemorrhage the bone marrow findings were similar to those found in the cases of iron deficiency anemias, namely, a hyperplastic marrow due principally to increased activity of the erythropoietic series with little or no leukopoietic changes. In those cases in which the blood loss had been great and rapid, in addition to a hyperactive erythropoietic marrow there was also observed some activity of the myeloid elements. This may account for the leukocytosis seen peripherally following this type of blood loss.

There were five such cases, two of extensive hemorrhages from bleeding peptic ulcers, two due to hemorrhage from the uterus, and one from hematemesis due to cirrhosis of the liver. The following case will be illustrative of this group. A young female with marked and severe uterine bleeding with a peripheral blood count of 39 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., and a slight leukocytosis, showed in her bone marrow smear: 2 megaloblasts, 21 erythroblasts, and 56 normoblasts per 100 white blood cells counted, a leukopoietic: erythropoietic ratio of 100:79. This returned to normal following treatment with blood transfusions, iron, and liver therapy. The marrow white cell elements showed a significant shift to the left, a finding absent in cases of slow hemorrhage.

Anemia of Thrombocytopenic Purpura. The anemia in this condition appears to be due to a non-specific blood loss. The marrow findings are similar to those in other cases of sudden great blood loss. We had one such patient, a young female, 13 years of age, with 38 per cent hemoglobin (Sahli), 2,000,000 red blood cells per cu. mm., 80,000 platelets in the peripheral blood, bleeding time of two hours with no clot retraction after 24 hours. Her marrow findings were the same as those of acute hemorrhage, namely, hyperplastic cellular erythropoietic elements with a slight increase in the

leukopoietic elements. She showed 4 megaloblasts, 15 erythroblasts, and 25 normoblasts per 100 white cells counted, a ratio of leukopoietic: erythropoietic elements of 100: 44. Cure was effected by splenectomy. Within two weeks her peripheral count and bone marrow findings were both normal.

It is of interest that some stress the significance of changes in the megakaryocytes in the marrow in essential thrombocytopenia. Splenectomy is considered by these workers to be curative if a normal number of megakaryocytes is present in the marrow, and to be of no value if megakaryocytes are markedly decreased or absent. Purpuras without marrow megakaryocytes are considered phases of aplasia of the marrow in which the platelet forming progenitors are not being formed, whereas if purpura exists and megakaryocytes are present in the marrow the lack of platelets in the peripheral blood is considered to be due to an inhibiting toxic substance elaborated in the spleen. Hence splenectomy is valuable in the one instance and useless in the other. Our patient had a normal number of megakaryocytes in her marrow and she responded promptly to splenectomy.

Anemia in Carcinoma. In these cases the bone marrow findings reflect largely the presence or absence of acute blood loss. There were eight cases of anemia associated with carcinoma, the peripheral counts ranging from 34 to 70 per cent hemoglobin (Sahli) with 1,800,000 to 3,500,000 red blood cells per cu. mm. The anemias were all of the normocytic type. Five of the eight cases had definite evidence of acute blood loss, either by melena, hematemesis, or hemoptysis. In these five cases the peripheral red blood cell counts were, as a rule, lower than in the others. Total marrow counts in them ranged from 65,000 to 170,000 nucleated cells, the erythropoietic elements showed definite increased normoblastic activity, and even the myeloid elements shared in the hyperplastic activity. These findings were the same as encountered in cases of sudden hemorrhage. In the three cases with no evidence of blood loss in which cachexia was a prominent feature, the bone marrows showed few qualitative changes from the normal. However, cellularity was definitely decreased. On this basis the bone marrow could be considered depressed probably as the result of some toxic factor associated with the carcinomatous process. The marrow counts in these three cases ranged between 19,000 and 28,000 nucleated cells. This diminished cellularity was shared alike by the erythropoietic and leukopoietic elements.

Anemia Due to Sulfanilamide. There were two cases of hemolytic anemia due to sulfanilamide. In one jaundice appeared suddenly in a patient taking sulfanilamide, accompanied by a fall in the blood to 48 per cent hemoglobin (Sahli) with 2,300,000 red blood cells per cu. mm., 24,000 leukocytes with 93 per cent neutrophiles, a reticulocyte count of 19.5 per cent, an icterus index of 63, and the presence of increased quantities of urobilinogen in the urine. The marrow findings in these two cases were similar, marked by a hyperplasia of all cellular elements more prominent in the erythropoietic series. There were 5 megaloblasts, 45 erythroblasts, and 72 normoblasts per 100 white blood cells, a leukopoietic: erythropoietic ratio of

100: 122. These results are similar to those reported in hemolytic anemias due to other causes.

We have also studied another case of hemolytic anemia which developed in a patient with polycythemia vera from phenylhydrazine hydrochloride intoxication. On admission to the hospital he was jaundiced, and his peripheral blood count showed 66 per cent hemoglobin (Sahli) with 3,190,000 red blood cells per cu. mm. His marrow findings indicated increased cellularity, active erythropoiesis at the normoblastic stage as in the previously described sulfanilamide hemolytic anemias, and a shift to the left of the myeloid elements.

There was one case of anemia resulting apparently from toxic doses of sulfanilamide but unaccompanied by hemolysis. Here, too, the marrow findings were hyperplastic and normoblastic.

Anemias Due to Infection. A few cases of infections were studied. In general these showed findings of no positive significance. Two cases of active atrophic arthritis in the acute stage showed little change from the normal. Two cases of acute glomerular-nephritis, one with uremia, showed unimportant changes. One case of active tuberculous adenitis with septicemia showed on repeated studies little change from the normal. One case of staphylococcic septicemia, aside from a slight shift to the left of the granulopoietic series, showed no other qualitative changes. Three cases of syphilis in latent stages showed no changes. Two cases of brucellosis showed nothing characteristic in the marrow.

Aplastic Anemia. We studied three such cases. From one no bone marrow could be obtained on puncture, and the condition was proved later to be an instance of sclerotic acellular marrow. The second case showed a marked acellularity on smear and count, and an absence of young forms of the erythropoietic series. In the third instance, a case of marble bone (Albers-Schoenberg's disease), the puncture yielded no marrow.

Chronic Benzol Poisoning. One such case had gone through a severe anemia simulating the aplastic type due to exposure to benzol in his occupation. At the time of examination his peripheral blood count had almost returned to normal, showing 74 per cent hemoglobin (Sahli), 3,700,000 red blood cells per cu. mm., and 7800 leukocytes with a differential of 34 per cent neutrophiles and 66 per cent lymphocytes. The bone marrow showed nothing significant.

Cooley's Anemia. A case of erythroblastic anemia in a six month old child showed a peripheral blood picture of 40 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., 13,000 leukocytes, with a normal differential, and 8800 nucleated red blood cells. The marrow reflected the erythroblastosis, the erythropoietic elements showing 10 megaloblasts, 47 erythroblasts, and 151 normoblasts per 100 white blood cells counted. The myeloid elements showed "the stimulating effect" by a shift to the left. The leukopoietic: erythropoietic ratio was 100: 208.

Polycythemia Vera. Six cases were studied, four before treatment with

phenylhydrazine hydrochloride. These four showed hemoglobin levels ranging from 140 to 180 per cent (Sahli), and from 7,400,000 to 9,000,000 red blood cells per cu. mm. Two were studied after treatment with phenylhydrazine hydrochloride which had restored the peripheral blood counts to normal values. The marrow puncture findings evidenced a moderately increased activity among the erythropoietic elements, normoblastic in type. These findings were little altered after treatment. The values were: 2.9 megaloblasts, 8.5 erythroblasts and 25.5 normoblasts per 100 white blood cells counted, a leukopoietic: erythropoietic ratio of 100: 37, a definite increase above normal. The lack of change after phenylhydrazine therapy may be taken as evidence that this hemolytic substance acts on the red blood cell mass in the periphery and not in the bone marrow. The granulopoietic cells showed no significant changes.

Conflicting reports on the marrow changes in polycythemia vera appear in the literature. Some have found no change even in the erythropoietic elements, whereas others have observed even greater normoblastosis in the marrow than our findings indicate.

Splenic Anemia. Three cases were so classified, cases of anemia of varying degrees with hepato-splenomegaly not conforming to any other recognized entity. In all, bone marrow studies showed no characteristic appearances.

Leukemia. In leukemia the marrow yields characteristic changes. In the diagnosis of this group of diseases marrow findings are most important. Especially is this true in what is termed "aleukemic" leukemia, a phase or species of leukemia in which the peripheral blood counts may be normal or inconclusive. In such instances the marrow usually reveals the existing state. In acute leukemia the marrow may yield diagnostic findings before characteristic peripheral blood appearances are obtainable. In chronic leukemia the marrow is usually confirmatory and corroborates the changes in the peripheral blood. In acute or leukopenic leukemia the bone marrow may be overrun with a large number of "blast" cells. In the presence of the nonspecific triad of leukopenia, thrombopenia, and anemia in the peripheral blood as often encountered in Banti's disease, pernicious anemia, essential thrombocytopenia, etc., sternal puncture aspiration may on occasions reveal the diagnostic findings of leukemia.

We have studied for orientation five cases of chronic myelogenous leukemia, all of which were previously diagnosed by peripheral blood examinations. All were confirmed by bone marrow studies. One of this group, a 78 year old male, was admitted to the hospital for rectal bleeding, anemia, and splenomegaly. The peripheral count showed a total of 170,000 white blood cells with 1 per cent myeloblasts, 1 per cent promyelocytes, 25 per cent myelocytes, 10 per cent metamyelocytes, 15 per cent non-segmented neutrophiles, 30 per cent segmented neutrophiles, 4 per cent basophiles, 1 per cent lymphocytes, 8 per cent eosinophiles, and 5 per cent eosinophilic myelocytes. Sternal marrow aspiration showed 330,000 nucleated cells with 4

per cent myeloblasts, 7 per cent promyelocytes, 26 per cent myelocytes, 17 per cent metamyelocytes, 18 per cent non-segmented neutrophiles, 18 per cent segmented neutrophiles, 4 per cent eosinophiles, 4 per cent eosinophilic myelocytes, 1 per cent basophiles, and 1 per cent lymphocytes. The red blood cell elements in the marrow were impoverished showing 0 megaloblasts, 0 erythroblasts, and 1 normoblast. The marrow findings in this case are typical of the others and correspond with the findings described by other workers. These findings consist of an increase of the total number of the white cell series crowding the bone marrow, and increase of the primitive and young forms of the myeloid series and a decrease of the erythropoietic elements.

In four cases of chronic lymphatic leukemia selected for study in which the diagnosis had been made by peripheral blood study, the bone marrow aspirations were confirmatory. One case will be illustrative of the group. A 40 year old female was admitted to the hospital for anemia, weakness and generalized lymphadenopathy. The peripheral blood count showed 230,000 leukocytes of which approximately 100 per cent were lymphocytes. The bone marrow aspiration yielded a total count of 280,000 nucleated cells with 100 per cent lymphocytes, some of which were lymphoblasts. There were scarcely any erythropoietic elements in the marrow smear.

In "aleukemic" leukemia bone marrow study finds its greatest usefulness. We studied five cases of acute leukemia of which four were leukopenic or "aleukemic." In these latter four the diagnosis was made by bone marrow study.

Case 1. S. F., male, 46 years of age, was admitted to the hospital for marked anemia, intermittent fever, chills, and an enlarged spleen of several weeks' duration. A peripheral blood count showed hemoglobin 38 per cent (Sahli), 1,500,000 red blood cells per cu. mm., 4500 leukocytes with 54 per cent neutrophiles and 46 per cent lymphocytes. The clinical diagnoses considered included: primary pernicious anemia, gastric carcinoma, typhoid fever, miliary tuberculosis, malaria, and acute bacterial endocarditis. In spite of all therapy he became worse. Two weeks later a sternal bone marrow aspiration showed a total count of 19,000 nucleated cells, with 40 per cent myeloblasts, 6 per cent promyelocytes, 16 per cent myelocytes, 9 per cent metamyelocytes, 9 per cent non-segmented neutrophiles, 3 per cent segmented neutrophiles, and 17 per cent lymphocytes. A definite diagnosis of acute myelogenous leukemia was thus established. The patient died after a few months, and the diagnosis was confirmed at autopsy.

Case 2. R. R., female, 13 years of age, was admitted to the hospital with a diagnosis of pneumonia because of chills, fever of 104° F., and anemia of acute onset. The hemoglobin was 36 per cent (Sahli), 1,400,000 red blood cells per cu. mm., 1900 white blood cells with 22 per cent neutrophiles and 78 per cent lymphocytes. Although leukemia was suspected no bone marrow puncture was done on this admission. She made a complete recovery clinically and hematologically on transfusions, and was discharged within four weeks with a peripheral blood count of 90 per cent hemoglobin (Sahli), 4,500,000 red blood cells per cu. mm., 8500 leukocytes with 47 per cent neutrophiles and 53 per cent lymphocytes. One month later she was readmitted with fever and weakness. The peripheral blood count was now 86 per cent hemoglobin (Sahli), 4,500,000 red blood cells per cu. mm., 9000 leukocytes with 46 per cent neu-

trophiles and 54 per cent lymphocytes. A bone marrow puncture at this time showed a total of 75,400 nucleated cells with 93 per cent "blasts." A definite diagnosis of acute leukopenic leukemia was thus established. The patient died within a few months and the diagnosis was confirmed at postmortem examination.

Case 3. B. C., female, 55 years of age, was admitted to the hospital for weakness, fever, weight loss, anemia and lymphadenopathy. Her peripheral blood count showed 1500 leukocytes with 50 per cent neutrophiles, 38 per cent lymphocytes, 3 per cent monocytes, and 9 per cent "blasts." Sternal puncture showed 15,500 nucleated cells of which 60 per cent were "blasts," probably monoblasts. The erythropoietic elements were strikingly diminished showing: 0 megaloblasts, 1 erythroblast, and 1 normoblast per 100 white blood cells. A diagnosis of acute leukemia was made. Later developments during life made the diagnosis of acute monoblastic leukemia possible, and this was proved at postmortem examination three months later.

Case 4. R. R., female, 60 years of age, was admitted to the hospital for ulceration of the gums and anemia. Her peripheral blood count showed 42 per cent hemoglobin (Sahli), 3,400,000 red blood cells per cu. mm., 1600 leukocytes with 15 per cent neutrophiles, 58 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles, 3 per cent basophiles, and 22 per cent atypical lymphocytes. Diagnoses of leukemia or primary pernicious anemia were considered. Bone marrow aspiration showed a total count of 42,000 nucleated cells with 71 per cent lymphoblasts, confirming the diagnosis of acute lymphatic leukemia. The erythropoietic elements were markedly decreased in the bone marrow.

Case 5. A. E., male, 15 years of age, was admitted to the hospital with fever of septic type, anemia, splenomegaly and lymphadenopathy. The peripheral count showed an anemia with a total leukocyte count of 45,000 of which 24 per cent were myeloblasts, 40 per cent promyelocytes, 10 per cent myelocytes, 8 per cent segmented neutrophiles, 5 per cent lymphocytes, 3 per cent monocytes, 9 per cent eosinophiles, and 1 per cent eosinophilic myelocytes. The sternal marrow confirmed the peripheral findings of acute leukemia. It showed a total count of 130,000 nucleated cells of which 63 per cent were myeloblasts, 3 per cent promyelocytes, 4 per cent myelocytes, 8 per cent metamyelocytes, 14 per cent neutrophiles, 6 per cent eosinophiles, 2 per cent lymphocytes, and a marked diminution of the erythropoietic elements.

These case reports indicate that marrow studies in acute leukemia will often disclose the condition long before it is reflected in the peripheral blood. In such cases the marrow is almost entirely replaced by "blast" cells. There is also a poverty of the erythropoietic elements, the result of either a crowding out of erythropoietic tissue or a depression of erythrogenesis. These cases also illustrate the difficulties of diagnosis in situations wherein anemia, fever, and leukopenia are present, and the invaluable aid bone marrow study can furnish.

Another case of leukemia worthy of mention was that of a 51-year-old female with chronic myelogenous leukemia receiving roentgen-ray therapy. On one occasion she was readmitted to the hospital for a severe attack of herpes zoster, at which time the peripheral blood count as a result of recent irradiation appeared essentially normal. A sternal puncture, however, showed a characteristic leukemic marrow well illustrating the point made by other workers [6] that in cases of leukemia treated with roentgen-ray the bone marrow findings may be identical with untreated cases although the peripheral count may be normal.

Infectious Mononucleosis. This disease, with its acute febrile onset, glandular enlargement, frequent splenomegaly, and leukocytosis with lymphocytosis may present a trying situation to the clinician until he is able to differentiate between it, a relatively harmless self-limited disease, and the hopeless state of acute leukemia. The heterophile antibody test appears to be of value in only about 50 per cent of cases. Any rapid dependable method of differentiating between these two diseases becomes a boon to clinical medicine, by permitting safe grounds for prognosis. The bone marrow study offers such a method.

In infectious mononucleosis the bone marrow yields no characteristic findings, but the presentation of essentially normal findings despite the great increase of leukocytes and lymphocytes in the peripheral blood definitely eliminates the diagnosis of leukemia. Since the lymphocytes in the peripheral blood in this disease are atypical, the bone marrow should be examined in all such cases.

We studied 11 cases of acute infectious mononucleosis. The peripheral counts ranged from 6,000 to 20,000 leukocytes with differential counts showing as high as 94 per cent lymphocytes. The marrow counts lay within normal ranges both for leukopoietic and erythropoietic elements. The average was as follows: Total counts from 20,000 to 170,000 nucleated cells. Differential count: 1 per cent myeloblasts, 2 per cent promyelocytes, 17 per cent myelocytes, 25 per cent metamyelocytes, 36 per cent neutrophiles, 13.7 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophiles, and 0.3 per cent reticulum cells; and 1 megaloblast, 5 erythroblasts, and 12 normoblasts per 100 white blood cells.

Thus, the finding of a normal bone marrow when infectious mononucleosis is suspected is sufficient to eliminate the possibility of leukemia. A hopeful prognosis may, therefore, be offered. The following case will illustrate this point. A.K., male, aged six years, was admitted to the hospital with fever, glandular enlargement, and splenomegaly of acute onset. The peripheral count showed 88 per cent hemoglobin (Sahli), 4,400,000 red blood cells per cu. mm., 12,500 leukocytes with 18 per cent neutrophiles and and 82 per cent lymphocytes. The clinical diagnosis rested between acute lymphatic leukemia and infectious mononucleosis. The sternal marrow showed 90,000 nucleated cells with 1 per cent myeloblasts, 2 per cent promyelocytes, 8 per cent myelocytes, 12 per cent metamyelocytes, 17 per cent non-segmented neutrophiles, 50 per cent segmented neutrophiles, and 10 per cent lymphocytes. The erythropoietic elements were present in normal numbers. The diagnosis of a normal active marrow eliminated the possibility of acute leukemia. The child made an uneventful recovery within three weeks.

Amidopyrine Granulopenia. An excellent example of the occasional effect of amidopyrine on the bone marrow in arresting maturation of the myeloid cell elements was furnished by the following case. N.G., female,

58 years of age, was admitted to the hospital because of painful joints. Her peripheral blood count showed 92 per cent hemoglobin (Sahli), 4,600,000 red blood cells per cu. mm., 6100 leukocytes with 70 per cent mature neutrophiles. During the course of hospitalization she was given one dose of 5 grains of amidopyrine for headache. The following morning she was prostrated, apathetic, and a peripheral leukocyte count showed 3200 white blood cells with 16 per cent mature neutrophiles. A bone marrow puncture at this time revealed a general decrease of the total white blood cells with failure of maturation, showing arrest in development at the myelocytic and metamyelocytic stages as follows: Total count 17,200 nucleated cells with 1 per cent myeloblasts, 2 per cent promyelocytes, 51 per cent myelocytes, 21 per cent metamyelocytes, 15 per cent non-segmented neutrophiles, 3 per cent segmented neutrophiles, and 7 per cent lymphocytes. Erythrogenesis was normal, showing the selectivity of the action of amidopyrine on the myeloid cells. Ten days later the bone marrow and peripheral blood counts were both normal.

Multiple Myelomata. In this disease the marrow findings are diagnostic, as shown by the following example. R.L., female, 30 years of age, had three admissions to the hospital within one year for severe anemia, hepatosplenomegaly, and ascites. Peripheral blood count was 35 per cent hemoglobin (Sahli), 1,600,000 red blood cells per cu. mm., with a normal white blood cell count and differential. On one occasion splenectomy was performed because of suspected Banti's disease. Later tuberculous peritonitis was diagnosed. With the roentgen-ray appearance of a few rarefied areas in the skull a diagnosis of multiple myelomata was considered and a sternal marrow puncture done. This showed 180,000 nucleated cells with 82 per cent myelomatous cells confirming the diagnosis. This was further proved at autopsy some months later.

Hodgkin's Disease. Three cases were studied. No characteristic changes were observed in the marrow. Other investigators have been able to make a diagnosis from marrow studies when bone involvement is present, by the finding of the Sternberg-Reed cells.

Trichinosis. Three cases were studied. All had eosinophilia, ranging from 22 to 66 per cent. All showed marked infiltration of the mature adult eosinophile in the marrow.

Malignancy. The marrow findings in carcinoma were discussed earlier in this paper. In sarcoma we found nothing characteristic in the marrow puncture. Some investigators have been able to diagnose the presence of malignancy by the chance finding of malignant cells in the marrow aspiration.

Negative Marrow Findings as an Aid in Diagnosis. This consisted of a group of miscellaneous cases with non-characteristic involvement of the reticulo-endothelial system, showing glandular enlargements, splenomegaly, variations from the normal in the peripheral blood counts such as anemia, leukocytosis or leukopenia, abnormalities in the differential smears such as lymphocytosis, increase in the young granulocytes, etc. In all such condi-

tions blood dyscrasias must be considered or eliminated before the correct diagnosis can be made.

There were 60 such cases. In all, the finding of normal marrow was indispensable in the elimination of diagnoses of specific blood dyscrasias. Several such patients are presented here for illustration.

Case 1. A. R., male, 47 years of age, was admitted to the hospital because of sepsis, temperature ranging to 104° F. daily, anemia, and an enlarged hard spleen of a few weeks' duration. The peripheral blood count showed 46 per cent hemoglobin (Sahli), 2,200,000 red blood cells per cu. mm., 10,200 leukocytes with 75 per cent neutrophiles, 24 per cent lymphocytes, and 1 per cent monocytes. Roentgen-ray of the chest showed some enlarged hilar glands. The clinical diagnoses considered were: "Aleukemic" leukemia, Hodgkin's disease, typhoid fever, and subacute bacterial endocarditis. A normal bone marrow study eliminated the diagnosis of leukemia. Histologic study of a gland revealed Hodgkin's disease. At postmortem examination several months later the latter diagnosis was confirmed.

Case 2. D. G., 60 years of age, was admitted to the hospital because of weakness, weight loss, generalized lymphadenopathy, and hepato-splenomegaly. No anemia was present, but the peripheral leukocytes ranged from 14,000 to 23,000 with 61 per cent lymphocytes. The diagnoses considered were lymphatic leukemia or carcinomatosis. The bone marrow puncture findings were normal. Subsequent clinical developments established a diagnosis of carcinoma. At postmortem examination carcinoma of the liver was found.

Case 3. H. L., female, 33 years of age, was admitted to the hospital because of fever, splenomegaly, anemia, and leukopenia. She had been treated in another hospital for pernicious anemia without benefit. She was suspected of having "aleukemic" leukemia but normal bone marrow findings discarded such a diagnosis. After a downhill course she died, and postmortem examination revealed carcinoma of the ovaries.

Case 4. J. B., female, 48 years of age, was admitted to the hospital because of dyspnea, ascites, anasarca, anemia and hepatomegaly. Portal cirrhosis, carcinomatosis, nephrosis, Hodgkin's disease, amyloidosis, and some form of blood dyscrasia were considered diagnostic possibilities. The peripheral blood count showed anemia and leukopenia. Normal bone marrow study eliminated a diagnosis of leukemia. At postmortem examination diffuse obliterative constrictive pericarditis was found.

Case 5. L. D., 48 years of age, was admitted to the hospital for pain in the left thigh which on roentgen-ray examination disclosed an osteolytic lesion suspected of being sarcoma, carcinoma, myeloma, or tuberculosis. Sternal puncture eliminated the diagnosis of multiple myeloma. Subsequent developments established a diagnosis of hypernephroma with metastasis to the femur.

Case 6. J. B., 50 years of age, was suspected of having multiple myeloma because of the roentgen-ray presence of rarefied areas in the humerus. Sternal puncture examination was negative for myeloma cells. Subsequent developments showed the case to be one of metastatic carcinoma.

Case 7. B. R., 27 years of age, was admitted to the hospital for weakness, anemia, lymphocytosis, splenomegaly and joint pains. Leukemia was suspected but eliminated by normal bone marrow findings. Later developments established a diagnosis of rheumatic fever.

Case 8. A. G., 58 years of age, male, was admitted to the hospital because of a disturbance in gait and pain in the lower back. Roentgen-ray examination disclosed an osteolytic lesion of the lumbar vertebrae with metastatic lesions of the pelvic bones. Carcinoma and multiple myeloma were considered in diagnosis. Bone marrow study was negative for myeloma cells. At operation for relief of pressure on the cord carcinoma was found.

Discussion

The value of any diagnostic procedure must be judged by the ease of its performance, its safety and the information it provides. Such considerations may outweigh absolute superiority of material. It is true that sternal biopsy provides a specimen more properly bone marrow than a marrow puncture, in that the former retains the architectural framework of the tissue and the unaltered relationship of its constituent parts. However, this procedure is a surgical one and has not for this reason been widely used. The tissue obtained requires the usual histologic treatment, involving delay in reporting and a special staining technic of some delicacy not constantly successful except in expert hands. In the majority of instances sternal puncture provides as much diagnostic information as the biopsy, since in most instances diagnosis can dependably be based on the types and relative percentage of cells observed in the smear. The staining of the smear is, moreover, as simple as that used in the ordinary differential count and is done as quickly. The cells in the marrow corresponding to those usually seen in the peripheral blood stain in the same manner and retain the same characteristics as those in the peripheral blood, and hence are easily recognized. Unusual cells have readily observable and reproducible characteristics.

In the few instances in which no adequate bone marrow can be obtained by puncture, biopsy should be resorted to. This may be necessary in cases of aplastic anemia with fibrotic or sclerotic marrows or in cases of marble bone disease in which no marrow is obtainable because of the nature of the underlying pathologic process.

We would like to stress that the great bulk of the cases presented represented problem cases in which the clinician sought aid from the procedure he ordered. Relatively few represent material obtained for study and preliminary orientation.

It will be seen from the data presented that the marrow puncture has great value in many conditions in both a positive and negative sense. It is virtually diagnostic in acute leukemia, "aleukemic" leukemia, and multiple myeloma. This also applies for leishmaniasis, malaria and Gaucher's disease. It is confirmatory in chronic leukemia in all its phases. In pernicious anemia it may help establish the nature of an obscure anemia, and will prove of great value in showing the potentialities of the bone marrow in respect to erythropoiesis and in evaluating therapy. In regard to potentialities we have found the marrow findings of value in estimating the reactive capacity of the bone marrow, particularly in anemias due to hemorrhage, and have on a few occasions been able to advise against transfusion because the marrow was hyperplastic and appeared inherently capable of generating sufficient cells to overcome an existing anemia unaided.

Bone marrow puncture is of inestimable value in a negative sense in a great host of conditions mimicking blood dyscrasias where the elimination of a specific blood dyscrasia is a matter of great import. Especially is this

true in infectious mononucleosis in which puncture enables one to offer a reassuring diagnosis and prognosis.

It should be stressed that in general the marrow findings, despite their specific character in certain diseases, should be regarded and evaluated as an additional finding, set in a general clinical composite. The bone marrow, like other tissues of the body, reflects the effects of pathologic processes elsewhere in the body and, because of the naturally limited varieties of response of which tissues are capable, may on occasions be the seat of changes approximating in degree or kind the abnormal specific changes representative of the true blood dyscrasias. That possibility should be no more confusing than similar difficulties in evaluating data in other diagnostic fields in which similar circumstances have arisen.

Conclusions

1. Bone marrow puncture is a simple, adequate and safe method of studying the living marrow. It is usable at all age periods and in all disease processes.

2. Bone marrow puncture is of inestimable value in the diagnosis and prognosis of diseases of the blood-forming organs.

3. It is of especial importance in excluding diseases of the blood-forming organs as a diagnostic possibility in many obscure conditions.

4. It provides material for an appraisal of the potentialities of the bone marrow.

5. It should, therefore, be considered as an essential adjunct in the study of any hematologic problem.

6. A series of 300 sternal punctures performed on nearly as many patients over a period of three years, chiefly in diagnostically uncertain cases, is presented to illustrate the above principles.

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A PATHOLOGICAL STUDY OF THE SIGNIFICANCE OF THE SYSTOLIC MURMUR*

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The subject of the systolic murmur is still a broad and rather unsettled phase of cardiology, and although much has been added to the general knowledge concerning the etiology and mechanics of this murmur, full progress and complete understanding in this important field have not kept pace with advances made in other branches of medicine. A search of the literature reveals a rather surprising number of divergent views which have been expressed regarding the cause, significance and interpretation of the systolic murmur.

The factors entering into the production of a murmur are well brought out by Sprague [2] who states "that a cardiac murmur is an audible vibration produced in the circulating blood by the formation of rhythmic eddies. These eddies are the result of a disturbance in the stream flow, produced where a region of discontinuity occurs when streams of different velocities are opposed. Such changes occur when a relatively narrow jet of fluid is projected into a vessel or chamber of wider diameter. To be audible the jet must have a velocity of a critical level and this is determined not only by the diameter of the stream but by the pressure difference behind and ahead of the constriction."

Although it is generally agreed at the present that the diastolic murmur, with rare exceptions, denotes a cardiac valvular pathologic lesion, the rôle and significance of the systolic murmur have not been fully established. The various opinions given concerning its value range from complete acceptance as a pathognomonic indication of an organic lesion to almost total disregard of it as an aid in the diagnosis of heart disease.

Auscultation, as a method in physical diagnosis, was first introduced by Laennec [1] in 1819. He revealed a surprising comprehension of heart sounds and expressed the opinion that all murmurs were positive indications of the presence of cardiac valvular lesions. Subsequently he denied these statements when he found that postmortem examination of such patients with murmurs failed in certain instances to reveal the lesions he anticipated.

In varying positions between these two opposite views expressed by Laennec range the conceptions of later workers, based on numerous clinical and experimental investigations. From these studies it became evident that the systolic murmurs were caused not only by deformities of the valves, but by other factors not clearly defined, and in some instances occurred in what seemed to be entirely normal hearts. This led to several classifications

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of the systolic murmur, the most familiar one dividing the cases into two categories, organic and functional.

Attempts to differentiate between organic and functional murmurs have been made repeatedly by many clinicians who have formulated criteria for that purpose.

Morse [4] contends that there is no certain distinction to be made between such murmurs. White [5] states that the louder a murmur the more likely it is to be organic.

Bass, Mond, Messelloff, and Oppenheimer [6] consider it of prime importance to make such differentiation and, after studying a large series of cases, found that most methods already in use were unreliable. They decided that differentiation could be accomplished best by phonocardiographic records.

Maliner [7] advised the use of subcutaneous injections of epinephrine for the same purpose and concluded that 71 per cent of children thought to have functional murmurs had in reality some underlying organic condition.

For a time the determination as to the presence of cardiac disease in a patient was limited in the main to a search for the presence or absence of murmurs. To emphasize the inadequacy of such methods MacKenzie [8] often advised throwing the stethoscope away entirely. Cabot [9] later wrote that the systolic murmur without the presence of other signs of heart disease was of no importance, and White remarks that most systolic murmurs do not indicate the presence of any organic heart disease. On the other hand, Levine [10] observes that a systolic murmur is not common in normal individuals and that louder ones are always associated with some form of cardiovascular disease. Further, all systolic murmurs deserve consideration, even if the patient looks well and has no symptoms or signs of cardiac insufficiency.

According to Herrick,[11] two important conditions in the heart may be betrayed by a systolic murmur—a rheumatic heart and beginning sclerosis in a valve. Some of the pathological and clinical factors recognized as causing systolic murmurs of the organic type are: stenosis or insufficiency of the valves; certain congenital deformities as patent *ductus Botalli,* patent interventricular septum, patent interauricular septum, muscular bands,[2] anomalous *chordae tendineae* and papillary muscles; vegetations and sclerotic changes of valves. Causes of functional murmurs are: stretching of valve rings, dilatation of chambers, hypertrophy, anemia, tachycardia, fever, and neurocirculatory asthenia. In addition to these factors Bystritsky, Zuelger, Lederer and Stolte [13] noted that systolic murmurs were produced in certain disorders of the myocardium and concluded that such murmurs may occur with decreased cardiac tonus and contraction. In the opinion of Zuelger [12] a systolic murmur may be the earliest indication of cardiac weakness. Friedlander and Brown [28] were able to show that not only exercise but certain drugs such as epinephrine were capable of producing a systolic murmur.

Therefore, the necessity for the early recognition of the nature of a murmur becomes at once apparent. In some instances a seemingly innocent

murmur may be owing to some remote organic change in the cardiovascular system, or it may indicate the potentialities for the subsequent development of manifest stenosis of the mitral valve,[10] or be an accompaniment of hypertension or subacute bacterial endocarditis. In young people it may be the only indication that the patient has had a rheumatic infection. Robey [14] cautions against the great harm that may result to a patient by making a diagnosis of cardiovascular disease on a murmur alone, and emphasizes the importance of properly evaluating a good history and other circulatory signs before the stethoscope is employed. On the other hand, many serious conditions may exist without the presence of a murmur, such as syphilitic aortitis, hypertensive heart disease, and coronary artery disease.

Fahr [15] conducted a study on a series of normal children and on an older group of individuals and found that 40 to 70 per cent of all children examined between the ages of six and 14 years and 35 per cent of otherwise normal older individuals in the second decade have murmurs. He adds that if no diastolic murmur appears during the first or second year following the last attack of rheumatic fever and if the size and shape of the heart have not changed significantly, the murmur is undoubtedly of no consequence. Levine [16] examined 1000 normal persons engaged in various occupations and found that 19.6 per cent of these presented a systolic murmur. In a group of university students, Reid [17] found 20 per cent with a systolic murmur. In a series of experiments on dogs, Thayer and McCollum [18] have shown that a systolic murmur can be produced at the pulmonary orifice by slight pressure of the stethoscope on the thin walled conus; and that bleeding and even subsequent intravenous infusion of salt solution might likewise be followed by this murmur.

It is obvious, therefore, from the above that the current clinical teaching which tends to disregard the significance of all systolic murmurs is just as unsound as the older view which associated every adventitious sound with organic disease. Somewhere between these two extremes lies the truth.

Many investigations have been carried out to substantiate these views, most of them on a clinical or experimental basis. Further investigation, from another approach, was therefore decided upon. Hence the present study was undertaken on a pathological basis, correlating the clinical observations with the subsequent pathological findings on postmortem examination.

Method

The records of Grasslands Hospital were examined, covering a period of five years from 1933 to 1938. The charts selected were those of all deaths in the hospital which had come to necropsy. Records which were incomplete, traumatic cases, and those patients whose stay in the hospital was not sufficient to permit of a complete physical examination and work-up were rejected. Of this group, all cases presenting a systolic murmur clinically were chosen. The final acceptance of the presence of a murmur was

carefully determined by comparing all notations and physical examinations made by the attending and house staffs. Any disagreement as to a murmur or failure to mention a murmur eliminated that chart from the study. The age, sex, history, physical findings, clinical diagnosis and postmortem examination were noted. Sub-groups were then made of etiological factors, history, valvular pathology, and other associated conditions.

The total number of cases examined in this study was 1148. Of this number, 268 or 23.1 per cent were found to have clinically one or more systolic murmurs. The apex proved the most frequent site of murmurs (222 instances). This was followed by the aortic area (61 instances), the pulmonic area (3 instances), and finally by the tricuspid area (1 instance).

Diastolic murmurs were associated with systolic murmurs 33 times. The final diagnoses in this group of 33 cases with associated diastolic murmurs included: 26 cases of valvular stenosis and insufficiency, three cases of aneurysm, and four cases of densely calcified valves.

The analysis of the records of this series of cases with systolic murmurs led to a subdivision of the cases into three groups according to the character of the findings which bore a relation to the occurrence of the murmur.

I. Pathological findings
   (*a*) valvular incompetence
   (*b*) valvular deformity
   (*c*) cardiac hypertrophy
II. Clinical findings
III. No findings

Pathological Findings

Sub-group (*a*): Of the 268 cases with systolic murmur either alone or associated with a diastolic murmur, 44 cases or 16.4 per cent were found in subgroup (*a*), comprised of cases showing evidence of valvular stenosis and insufficiency. This group was further subdivided according to etiology as follows:

a. Rheumatic	21 cases or	47.7 per cent
b. Arteriosclerotic	14 cases or	31.8 " "
c. Syphilitic	5 cases or	11.3 " "
d. Congenital	4 cases or	9.1 " "
Total	44 cases	

Cases placed in the rheumatic group had all given a history of one or more attacks of rheumatic fever at one time. The various valvular lesions occurred in the following order of frequency:

1. Mitral stenosis	21
2. Mitral insufficiency	7
3. Aortic stenosis	2
4. Aortic insufficiency	2
5. Tricuspid insufficiency	1

Mitral stenosis, therefore, occurred in all cases, either alone or in combination with other lesions. It occurred together with mitral insufficiency seven times, but mitral insufficiency never occurred alone. Aortic stenosis and aortic insufficiency also were twice noted associated with mitral stenosis, but were not observed as single lesions. Tricuspid insufficiency was seen once and then occurred in combination with mitral stenosis.

The age limits of these patients were interesting. The oldest patient in this series was 60 years old, the youngest was 4. However, one patient was 51, another 40, and five patients were in their thirties. The average age of these persons was 26.1 years. Death in all cases resulted from heart disease and this was clinically diagnosed. There were three cases of subacute bacterial endocarditis.

The *arteriosclerotic* group followed the rheumatic group as to the number of valvular lesions with 14 cases or 31.8 per cent. The order of frequency of these lesions was as follows:

1. Aortic stenosis 8
2. Mitral stenosis 6
3. Mitral insufficiency 3
4. Aortic insufficiency 2

Aortic stenosis was the most frequent valvular condition found in arteriosclerosis. It occurred with aortic insufficiency once. However, it did not occur in all cases as in the rheumatic group. Mitral stenosis was seen with mitral insufficiency occurring without aortic involvement.

All cases presented advanced clinical arteriosclerotic changes elsewhere in the body. The ages of these patients ranged from 86 for the oldest to 45 for the youngest, with an age average of 71.1 years. In this group the majority of cases, eight in number, died of arteriosclerotic heart disease, but the remaining six died of other causes which included malignancy, pyonephrosis, and fracture of the femur.

The *syphilitic* group was the third largest group with five cases. The frequency of the lesions found was:

1. Aortic insufficiency 4
2. Aortic stenosis 3
3. Mitral stenosis 1

Aortic insufficiency was the most frequent valvular condition encountered in syphilis, occurring four times. Aortic stenosis was noted three times and mitral stenosis once. The latter two did not occur alone but in combination with aortic insufficiency. The blood Wassermann was four plus positive in all cases, and in four cases there were clinical manifestations of syphilis elsewhere. The ages of these patients ranged from 77 to 32 years. The average age was 57.7 years. Death in these cases resulted in all instances from syphilitic heart disease.

The *congenital* group numbered four and represented the smallest group of cases of valvular heart disease, although it numbered only one less than the syphilitic group. These were all diagnosed as having congenital de-

fects and with one exception died as a result of the lesion. The single exception died of anemia. The frequency with which these lesions occurred was:

1. Patent foramen ovale 3
2. Patent *ductus Botalli* 1

The ages of these patients were two months to four years, with an average of 1.2 years.

In the second group of pathological changes fell a large number of valvular abnormalities which were not sufficient to cause incompetence of the valve, but nevertheless revealed deformities which were sufficient to produce murmurs mechanically. These cases numbered 136 or 50.7 per cent and the nature of these changes follows:

1. Sclerotic valves	47
2. Thickened valves	33
3. Calcified valves	24
4. Stretched valves	13
5. Scarred valves	7
6. Vegetations on valves	7
7. Nodules on valves	5
Total	136 or 50.7 per cent

More than half of all murmurs, therefore, fell into this group. These individuals were, with few exceptions, elderly people, the oldest being 97, and the average age 73.4 years. Deaths resulted from arteriosclerotic heart disease and hypertensive heart disease in 37 cases, vascular accidents in 11 cases, and in the remainder from miscellaneous causes.

Aneurysm was found in four cases or 1.4 per cent. These were found in the ascending aorta and the aortic arch. They were divided as follows:

1. Arteriosclerotic	3 cases
2. Syphilitic	1 case
Total	4 or 1.4 per cent

The syphilitic patient was 45 years old, whereas the arteriosclerotics were 61, 69 and 85 years old with an average of 71.6 years. Two were diagnosed before death. Of the other two cases, one was designated as vascular collapse and the other occurred undiagnosed in a patient with psychosis. Hypertrophy of the heart without any valvular abnormality was noted 25 times or in 9.3 per cent. The ages ranged from 97 to 27 with an average of 61.2 years. These comprised mainly miscellaneous cases.

There were, therefore, 209 cases or 78.2 per cent for whose murmurs some pathological explanation was found.

In the remaining 49 cases or 18.1 per cent, the examination revealed no anatomical basis for the presence of murmurs; however, the clinical history disclosed certain conditions which were known to produce murmurs. These were as follows:

1. Fever	21	cases
2. Hypertension	15	
3. Anemia	10	
4. Tachycardia	3	
Total	49	cases or 18.1 per cent

Finally, in the remaining 10 cases or 3.7 per cent no evidence, either clinical or pathological, was found to account for the systolic murmurs.

The sexes were practically equally represented in the cases showing systolic murmurs, the males comprising 50.2 per cent and the females 49.8 per cent.

Conclusions

The present study comprises an examination of the autopsy records of 1148 consecutive cases of whom 268 cases or 23.1 per cent had manifested systolic murmurs. Only 16.4 per cent of the cases with systolic murmurs presented actual evidence of valvular incompetence. The etiologic factors in this series proved to be rheumatic fever, arteriosclerosis, syphilis and congenital malformations in the order named. It was further observed that these patients all exhibited additional signs and symptoms of cardiac involvement. Among these were precordial thrills; diastolic murmurs, blood pressure changes, cardiac enlargement and a positive serological reaction for syphilis. In the rheumatic group a history of one or more attacks of rheumatic fever was elicited. This tended to emphasize the value of a careful history and close observation for other features of valvular stenosis and insufficiency. Thus the discovery of a systolic murmur not accompanied by any of the above characteristics must be viewed with caution from a diagnostic and prognostic standpoint. Characteristic lesions were found representative of each group. They were mitral stenosis in rheumatic hearts, aortic stenosis in arteriosclerotic cases, aortic insufficiency in syphilitic cases, and patent foramen ovale in the congenital group. However, it was noteworthy that except for limitation of a patent foramen ovale to the congenital group the other lesions occurred in any of the other groups.

The largest group in this series comprised 136 cases or 50.7 per cent. These cases were found to present pathologically various types and stages of valvular deformity. Although anatomically these valves were still competent, yet physiologically they were capable of murmur production. Here were noted various stages of sclerosis of the valves: vegetations, nodules and calcification of the valve leaflets or valve ring, as well as stretched and

scarred valves. Apparently some of these conditions represent mid-stages of rheumatic involvement of the endocardium as indicated by the finding of vegetations and nodules. On the other hand the thickening, calcification and scarring appeared to represent various degrees of arteriosclerotic change, which in some manner became arrested and did not proceed quite to the production of actual valve incompetence. Hence, although the systolic murmurs in this type of case resulted from a definite pathological change in the endocardium, they were classified generally as belonging to the functional group of murmurs. It was likewise noted that these conditions were compatible with long life, the average age at death being 73.4 years, with the oldest patient 97 years.

Aneurysm and cardiac hypertrophy also represented small groups of anatomically explained murmurs.

In a group of 18.1 per cent of cases the appearance of systolic murmurs was attributed either to fever, tachycardia, anemia or hypertension. These cases were anatomically normal.

Finally, in 10 cases or 3.7 per cent no clinical or pathological explanation for these murmurs was found.

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NEUROBLASTOMA (SYMPATHOBLASTOMA OR NEUROCYTOMA) OF THE SUPRARENAL MEDULLA; REPORT OF THREE CASES *

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THE sympathetic nervous tissue comprising the medullary portion of the suprarenal gland is the site of a relatively rare and spectacular group of tumors. In the past this subject has received some prominence in the medical literature, various writers having stated that cases are rare.

Tumors derived from the sympathetic nervous system of the suprarenal medulla may be divided into three well defined pathologic types, namely: (*a*) Neuroblastoma (sympathoblastoma or neurocytoma); (*b*) ganglioneuroma (neuroma ganglionare); (*c*) paraganglioma (chromaffin cell tumors). In this paper, along with the cases reported, discussion will be limited principally to the suprarenal neuroblastoma which occurs almost entirely in infants and children, and only occasionally in young adults. These cases constitute a definite pathologic entity, the clinical picture of which is quite varied and severe, as they always terminate fatally.

Virchow,[1] in 1864, was the first to study and report a case of primary malignant tumor of the suprarenal gland in children and designated it a glioma. Marchand,[2] in 1891 described a similar cellular tumor in an infant nine months of age and attributed the origin to the sympathetic nervous system. Kuster,[3] in 1905, described a cellular neoplasm of the suprarenal gland in an infant of 14 weeks which he interpreted as neuro-epithelial in origin, and at the same time described the characteristic alveolar rosette structures which are common to some of these tumors. In the literature these neoplasms have frequently been referred to as gliomas, round cell sarcomas and lymphosarcomas. In 1910 J. H. Wright [4] presented an excellent description of these tumors and rather definitely stated that they were of neuroblastic origin. Frew,[5] in 1910, reported several cases of neuroblastoma, several of which he collected from the literature. These he called carcinomas of the suprarenal medulla. Wahl [6] in 1914, Dunn [7] in 1915, Lehman [8] in 1917, Scott, Oliver and Oliver [9] in 1933, Lewis and Geschickter [10] in 1934, and Redman, et al.[11] in 1938, have contributed greatly to our present knowledge of these new growths and have added cases to the literature.

A better understanding of the neoplasms of the suprarenal medulla can best be obtained after reviewing the embryogenesis of the organ. The suprarenal gland consists of an outer cortical zone (interrenal organ) derived

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from the celomic epithelium, and a central medullary zone (suprarenal organ) which arises from the celiac sympathetic plexus and so is composed of sympatho-chromaffin tissue. The cortex develops earlier than the medulla, and in embryos of 9 mm. buds of cells from the celomic epithelium at the root of the mesentery become detached to form the suprarenal ridge. At 12 mm. the cortical portion is large. The medulla of the gland is formed by the primordial chromaffin cells which are termed neuroblasts or sympathogones. These cells emanate from the neural crest and migrate from

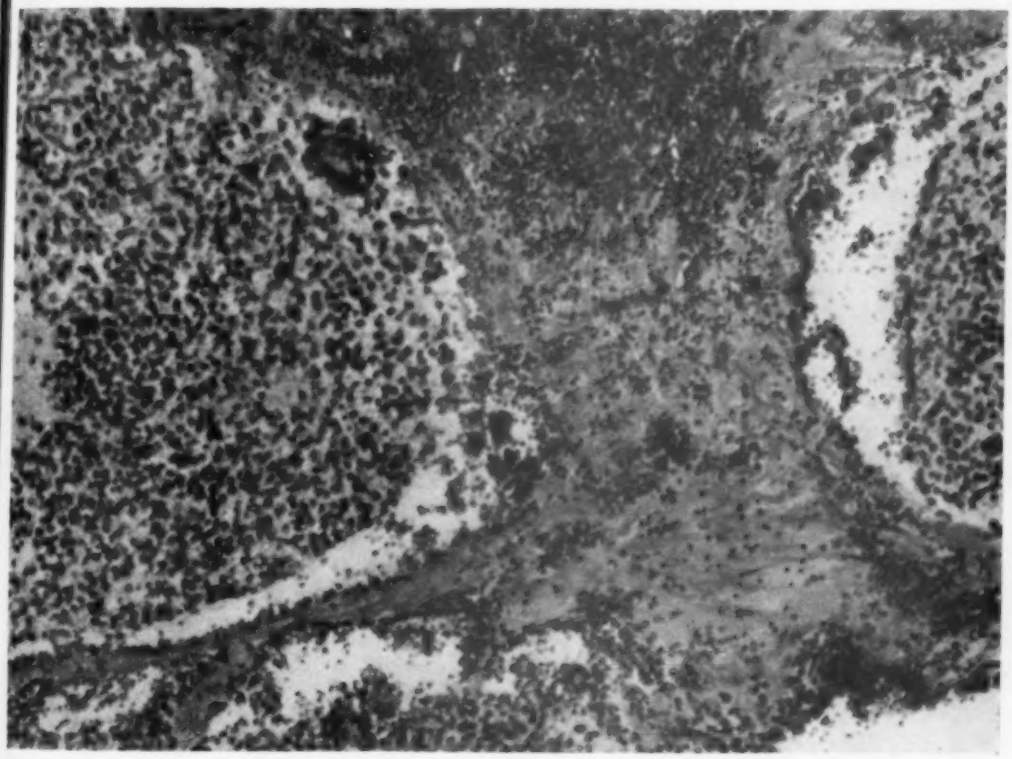

FIG. 1. *Case 1.* Microphotograph of neuroblastoma showing neurocytes, fibrillar matrix and an atypical rosette in the upper left quadrant. Hematoxylin and eosin stain. × 205. (U. S. Army Medical Museum Neg. No. 68988.)

the celiac plexus to the centers of the cortical masses. This migration begins at about the 19 mm. stage and continues until after birth. During migration the cells are immature and indifferent. Later the neuroblast or sympathogone develops either into the sympathoblast (neuroblast) or the phaeochromoblast and, in the further development, the sympathoblast is the precursor of the adult sympathetic ganglion cell, whereas the phaeochromoblast becomes the parent of the phaeochromocyte. As a consequence of distinguishing these various type cells emanating from the sympathogone, we can recognize and understand better the three types of medullary supra-

renal tumors previously mentioned as well as the allied tumors of the paraganglia and carotid body whose cells are similarly derived.

Thus, it is noted that the suprarenal cortex is of mesoderm origin whereas the medulla is of ectoderm origin; also, that tumors of the undifferentiated and immature neuroblasts may well be termed neuroblastomas, whereas those made up of the more differentiated, mature cells and fibers are called ganglioneuromas, and those formed from the chromaffin cells are called paragangliomas or phaeochromocytomas.

The paragangliomas or chromaffin cell tumors occur almost entirely in the third to sixth decades of life. They are quite rare, relatively benign in character, and histologically appear quite varied. These tumors of the suprarenal are quite similar to those chromaffin cell tumors that occur in other locations, for example, the carotid body, paraganglia and gastrointestinal tract. These latter tumors are frequently called argentaffin or carcinoid tumors. Neoplasms of the chromaffin tissue of the suprarenal contain cells in various stages of differentiation. The most common element is the large polygonal cell which frequently assumes a characteristic brown granular color after fixation in chrome salts, this reaction being constant in only the mature cells. These tumors are small, often encapsulated, frequently bilateral, and are usually accidental findings at autopsy. Metastases have been described. The growth presents small masses of round, oval and polygonal cells with occasional giant cells having single or multiple nuclei. The pigment is irregular, and at times the cells show very definitely their chromaffin nature after fixation in solutions of chrome salts.

The ganglioneuromas, first described in 1881 by Weichselbaum,[12] may occur at any age but are quite rare after 40. This tumor is not so common as the neuroblastoma. It arises from well differentiated sympathetic nerve tissue, and is relatively benign in character. It may reach considerable dimensions. The histologic picture shows a preponderance of medullated and non-medullated nerve fibers in which are masses or islands of well formed ganglion cells. Fibrous tissue may be present in varying amounts according to some writers.

The neuroblastoma or neurocytoma is by far the most common of the tumors originating in the suprarenal medulla, and occurs chiefly in children and young adults. It is related to the retinoblastoma of the eye and the medulloblastoma of the cerebellum. In 1933 Scott, Oliver and Oliver,[9] reviewed the literature and reported a total of 98 cases of sympathoblastoma (neuroblastoma) of which four were their own. In 1938 Redman, Agerty, Barthmaier and Fisher[11] reported finding an additional 113 cases. Since then a few other cases have been reported, bringing the total number of cases to about 220. Even with this number reported, these tumors are considered rare.

In an analysis of all cases reported the males predominated over the females in the ratio of 4 to 3, which is not highly significant. Because the

majority of cases occur in children under the age of five years, little emphasis can be placed upon other etiologic factors, such as trauma and previous afflictions.

In the literature two distinct clinical syndromes caused by this tumor are described, both of which are based upon the location of the metastatic lesions. These are termed the Pepper and Hutchinson syndromes and practically all writers attempt to classify their cases in one or the other of these, the reasons for which are not clear.

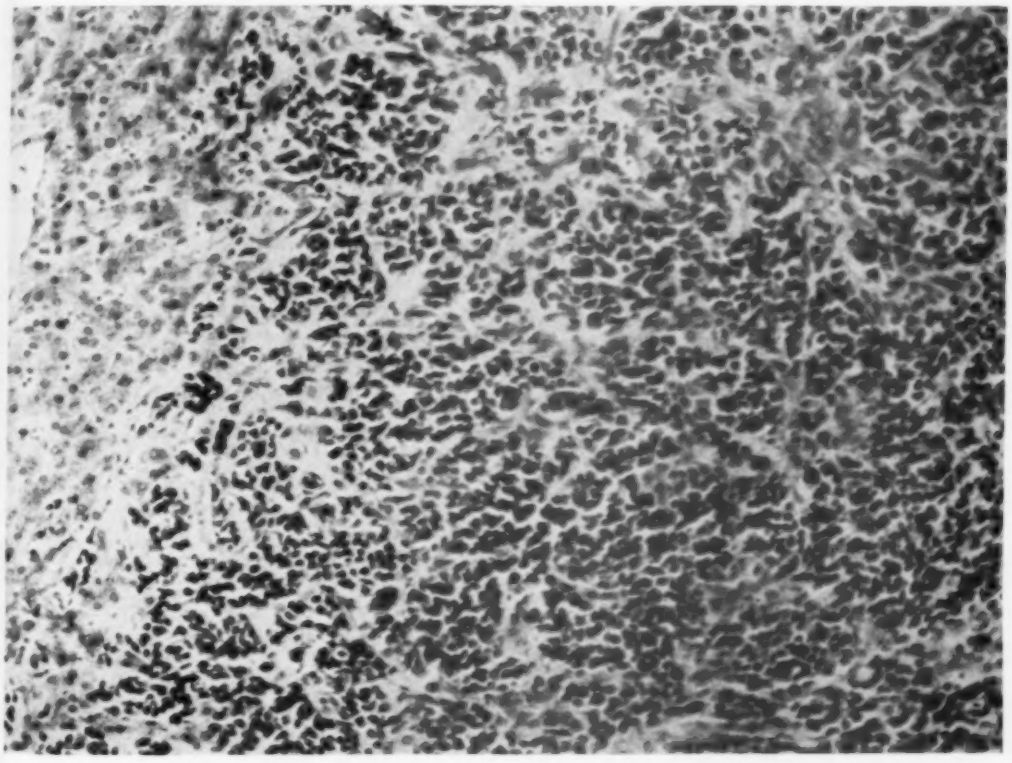

FIG. 2. *Case 2.* Microphotograph of neuroblastoma, a metastatic lesion of the liver, showing the fibrillar matrix about groups of small spindle and polygonal shaped cells with hyperchromatic nuclei. Hematoxylin and eosin stain. × 205. (U. S. Army Medical Museum Neg. No. 68990.)

Pepper,[13] in 1901, described six cases of neuroblastoma of the suprarenal medulla which he called round cell or lymphosarcoma. One of these cases was his own and the other five he collected from the literature. These six cases showed similarity in that they all occurred in females from 3 to 11 weeks of age and all showed marked liver metastases. None of these cases showed any metastases to bone. Three cases were primary in the right gland, one in the left, one was bilateral, and in one case no location was recorded. Therefore, it is suggested that a neuroblastoma of the suprarenal

gland in very young infants, occurring in one or the other organs with liver metastases only, be classified as one of the Pepper type. The liver metastases from the right suprarenal are apparently by extension.

Hutchinson,[14] in 1907, described 10 cases of suprarenal "sarcoma" in children from three months to nine years of age and emphasized the fact that metastases occurred in the bones of the skull and that all cases occurred spontaneously after trauma. He noted the presence of ecchymosis of the periorbital soft tissue followed by exophthalmos, tumor of the orbital bones, and metastases to the auricular and submaxillary lymph nodes. He described a secondary anemia in all cases but failed to mention the leukocytic picture. At autopsy a suprarenal medullar tumor was found on the left side in six cases and on the right in four, the growth varying in size from that of a small walnut to that of a child's head. He also mentioned that metastases are sometimes found in the ribs, sternum and vertebrae but was doubtful as to their presence in the long bones.

From a survey of the cases reported it is believed that entirely too much emphasis has and is being placed upon these two syndromes because features of both are noted in many of the cases and also, in many, the salient features are absent. In the literature the cases which show a great deal of overlapping of various criteria are listed as "unclassified," and about 20 per cent of the cases reported fall into this category. In our second case which occurred in a male child, aged five years, the tumor was primary in the right suprarenal, extended to the liver, and showed widespread bone metastases. Our third case simulated the Pepper syndrome with the exception that it occurred in a young, adult male, aged 18 years.

Frew,[5] in 1910, attempted to analyze the clinical pictures of both the so-called Pepper and Hutchinson syndromes by the presumed metastatic routes and stated that tumors originating in the left suprarenal gland metastasize, by means of the blood stream, to the skull, lungs and long bones, whereas those of the right gland, by means of the lymphatics travel to the liver and regional lymph nodes.

It is noted that the vein and lymphatics from the right suprarenal gland run from the upper pole to join the vena cava and main lymphatic trunk, whereas those of the left gland emerge from the lower pole to join with the renal vein and lymphatics.

The symptoms of neuroblastoma are quite varied and depend almost entirely upon the size and position of the primary tumor and their metastatic lesions. Again, since so many cases occur in infants and very young children, exact symptoms and their chronology are frequently difficult to ascertain. In a great many cases it is the parent who, while routinely caring for the child, notices something unusual and so consults a physician. In our case 1 the mother noticed a sudden appearance of right periorbital ecchymosis which prompted her to seek medical aid. In our case 2 the first sign that the child was ill was the fact that he frequently awakened and cried out at night. In our third case the patient developed abdominal pain with

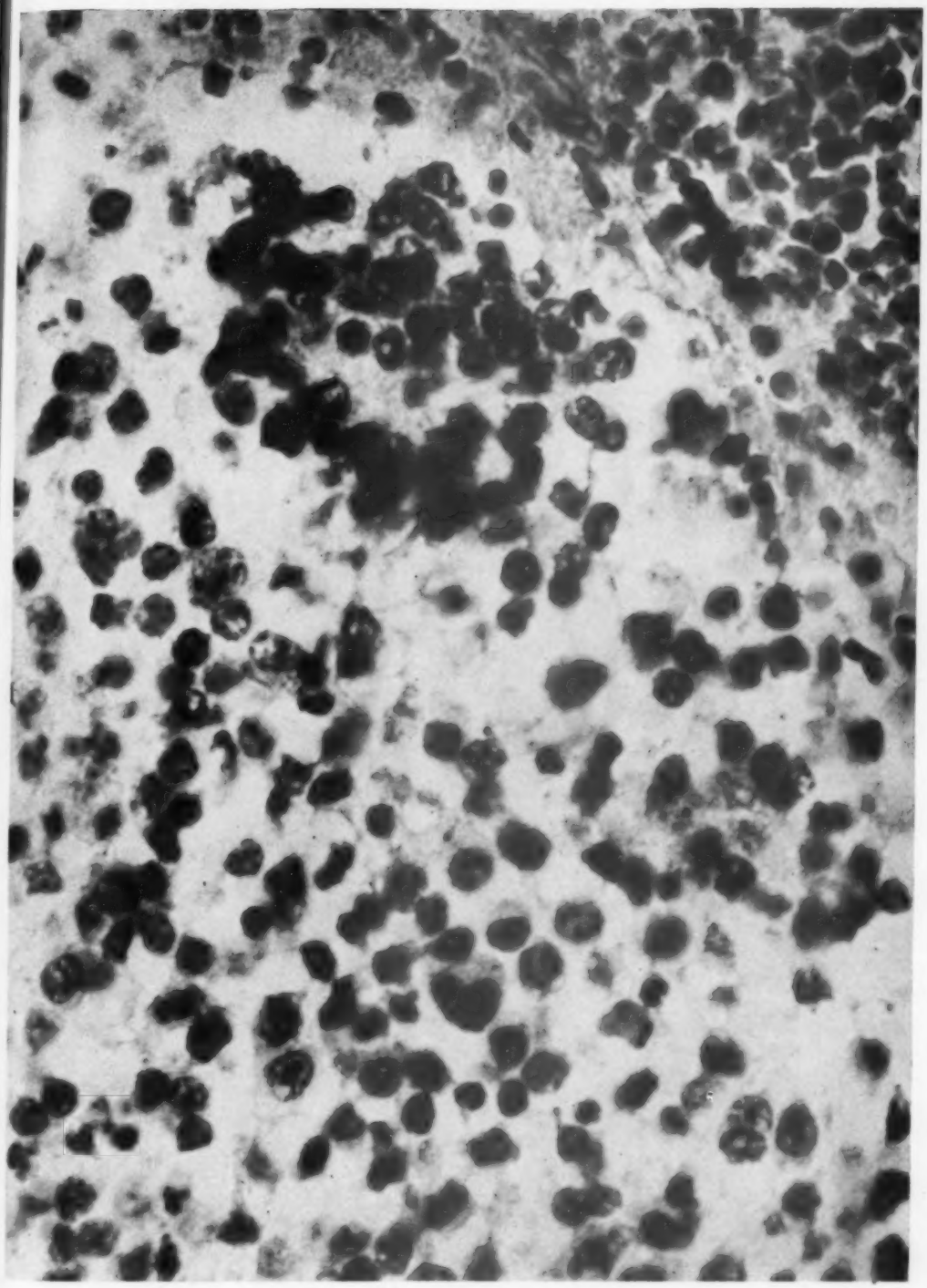

FIG. 3. *Case 1.* High magnification microphotograph of a field in figure 1 showing the atypical rosette and the character of the cells. Note the round, highly undifferentiated cells with hyperchromatic and vesicular nuclei which characterized the cell picture of neuroblastoma found in very young infants. An occasional large, mononuclear cell is seen representing a more mature type of neurocyte. Hematoxylin and eosin stain. × 1000. (U. S. Army Medical Museum Neg. No. 68991.)

nausea and vomiting; a diagnosis of "appendicitis" was made, and an appendectomy was performed.

Shortly after the onset of symptoms most patients develop an abdominal mass on one side or the other which becomes tender and slightly painful. Nausea and vomiting occur frequently. A secondary anemia is quite constant. Fever usually ranges from 99 to 104 degrees F. Pains in affected joints and bones are common, and in many cases exophthalmos with surrounding discoloration of the lids is noted. Diminished activity, pallor, dyspnea, anorexia and emaciation practically always occur, and these become more pronounced as the disease progresses. Lymphadenopathy, in various locations, is usual.

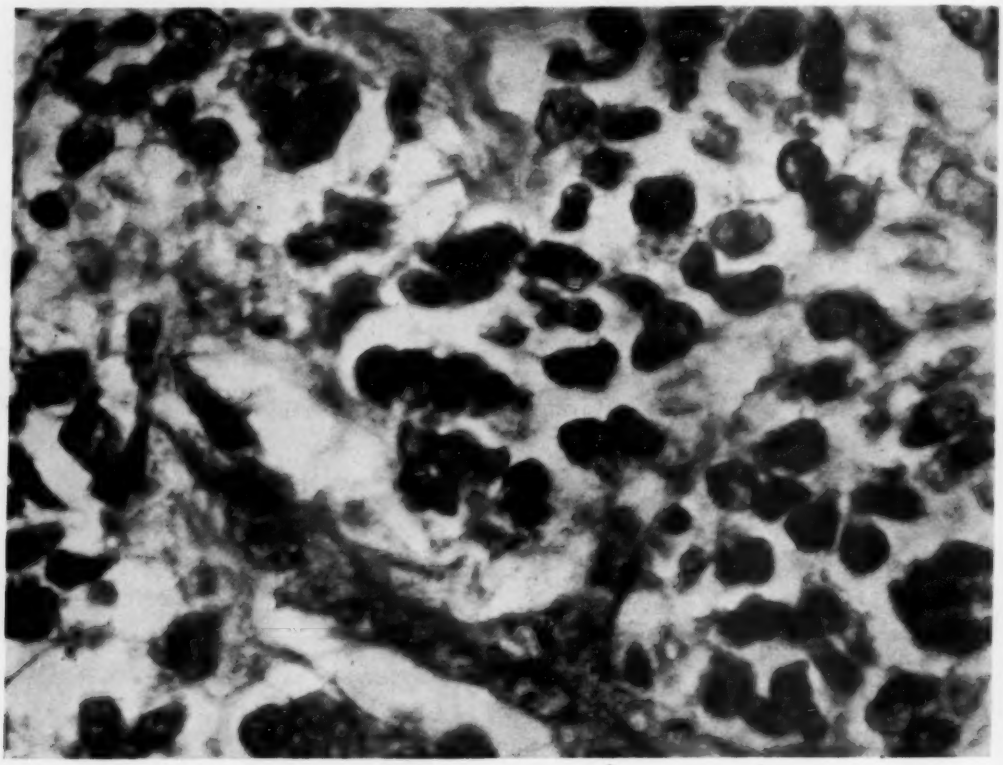

FIG. 4. *Case 2.* High magnification microphotograph of a field in figure 2 showing the spindle and polygonal shaped neuroblasts surrounded by the fibrillar matrix. The nuclei are hyperchromatic and vesicular. An occasional large multinucleated cell is noted. This type cell picture represents a more mature development of the neuroblast and is noted in older children and young adults. Compare with figure 3. Hematoxylin and eosin stain. × 1000. (U. S. Army Medical Museum Neg. No. 68992.)

The usual clinical course for this neoplasm is progressively downward, eventually terminating fatally. The number of days' hospitalization in our cases were 40, 191 and 105 days respectively.

The roentgen-ray findings in bone metastases are typical according to Lewis and Geschickter.[10] Scattered, small, multiple areas of rarefaction are usually seen. Of the bones in the body, those of the skull are the most common sites for metastases. The ribs, humerus and femur are commonly affected. In the skull the usual picture is separation of the sutures with scattered small areas of resorption, particularly in the frontal and parietal bones. The metaphysial areas of the long bones are usually the first affected

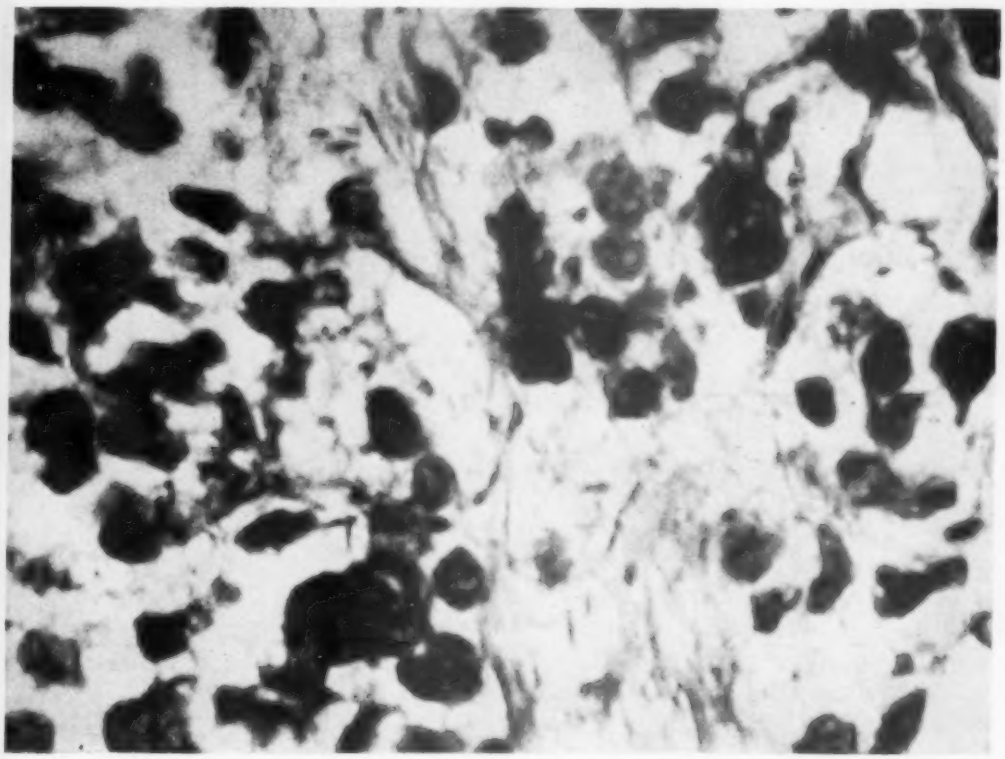

FIG. 5 *Case 2.* High magnification microphotograph of a field in figure 2 stained with Mallory's phosphotungstic acid hematoxylin method showing the axon-like processes of the cells and the fibrillar matrix. Note the single cell in the upper left quadrant with process pointing to lower right corner. × 1000. (U. S. Army Medical Museum Neg. No. 68993.)

and the areas of resorption are usually wedge-shaped in appearance. There is frequently an overlying periosteal reaction.

The diagnosis of neuroblastoma depends largely upon the metastatic lesions and the presence of an abdominal tumor. In those cases of orbital metastases, with exophthalmos and periorbital ecchymosis, the diagnosis is comparatively easy. The metastatic lesions present a histologic picture identical with that of the primary neoplasm. Contrary to the opinion of many, these tumors are sensitive to irradiation and melt down quite rapidly.

In lymphocytoma, including the leukemic forms, ascites and involvement of the superficial lymph nodes are usual findings. In neuroblastoma ascites almost never occurs.

Kidney tumors, with the exception of the Wilms' tumor, are rare in children and in this latter neoplasm, hematuria and urinary obstruction, along with significant pyelograms, are usually diagnostic. The Wilms' tumor does not metastasize to bones.

Thorough hematologic examinations will usually rule out chloroma, and this disease is rare in children. These studies of the blood, together with lipoid studies, examination of the spleen and roentgenograms, aid in the differentiation of Hand-Schüller-Christian disease.

Ewing's tumor seldom occurs before the age of four years and in the bony metastases the characteristic periosteal reaction with the onion peel splitting of the layers is usually present.

Acute surgical abdominal diseases are sometimes confused with neuroblastoma of the suprarenal medulla, but these are usually ruled out with ease after the entire examination of the patient is accomplished. In our third case the symptoms and signs indicated an attack of acute appendicitis for which an appendectomy was performed. Shortly after the appendectomy the abdominal mass became apparent, all signs and symptoms suggested a liver or subdiaphragmatic abscess, and further surgical measures were instituted.

Two of our cases were primary in the right suprarenal gland, and the other occurred in the left. Bilateral involvement has been recorded in several cases in the literature. The size of the tumor is quite variable and is dependent somewhat upon previous irradiation. The neoplasms are usually encapsulated and nodular and they may be solid or cystic. On cut section, the cut surfaces are usually yellowish-red and hemorrhagic, showing scattered areas of necrosis and hemorrhage. The kidney below the tumor mass is usually compressed and only rarely invaded.

The histologic picture of these tumors is quite characteristic. They are very cellular, the cells being of the small round, mononuclear type, containing very little cytoplasm and a large central, hyperchromatic nucleus. These cells occur in small masses or islands separated by strands or trabeculae of fibrils. This fibrillated stroma may be dense in areas and appear as hyaline, fibrous strands. In about 50 per cent of the cases rosette formation (the circular grouping of the cells about a central fibrillated stroma) is noted, but this feature is not as constant as in cases of retinoblastoma of the eye. Pseudo-rosettes (the grouping of cells about small capillaries) have been reported, but this histologic feature was absent in our three cases. Scattered among the small cells are occasional large, round to polygonal spindle shaped cells with vesicular nuclei. These cells have the appearance of the more mature type spongioblast. Occasionally mature ganglion cells or chromaffin cells are present which emphasize their relationship to the small, immature

neuroblasts. Occasionally fibrils, simulating axones, are noted arising from some of the tumor cells and are seen best with the Bielschowsky's neurofibril stain.[15]

It is generally concluded that the younger the patient, the less differentiated are the cells in the composition of the tumor, and likewise the greater the malignancy. In the very young the tumor is practically composed of the small round, immature, undifferentiated neuroblasts, while in older children and young adults the cells become polygonal and spindle-shaped, showing a tendency to form the more mature type cells. This feature is noted in comparing our first and second cases.

Multiple tumors of the sympathetic nervous system do occur which illustrate the three types of growth arising from the sympathetic system and represent the three stages in differentiation of the formative neuroblast, namely the neuroblastoma, ganglioneuroma and paraganglioma. Recently, Wahl and Craig,[16] in 1938, reported a case.

As stated previously in this paper, contrary to the opinions of many investigators, irradiation definitely affects these neoplasms. After irradiation the tumors definitely melt down and the life of the patient is prolonged. Although irradiation alters the size and consistency of the tumor, it does not halt metastases. Our second case received a total of 14,500 R and the abdominal mass melted from the size of a child's head down to the point where the tumor, at autopsy, measured 3 by 1.5 by 1.5 cm. The life of this patient was undoubtedly prolonged by the irradiation; however, one of the principal findings at autopsy was the marked aplasia or destruction of the bone marrow. The total leukocyte count just prior to death was 100. Surgery has been attempted in many cases but it is considered to be ineffective. Lehman,[8] in 1917, reported a case in which a neuroblastoma of the suprarenal medulla was removed in 1916, and the patient was reported well in 1931, 15 years after removal of the neoplasm.

Case Reports

Case 1. A. K., female, aged 17 months, entered W. R. G. Hospital on July 24 and died on September 2, 1939. The chief complaint was abdominal distress and bilateral periorbital ecchymosis. The apparent onset of symptoms was about July 1, 1939, at which time she developed a blue discoloration about the right eye. This was followed shortly by protrusion of the eyeball and a spread of the discoloration to the tissues about the left eye.

The family history was not remarkable except that her maternal grandmother had died of carcinoma of the bladder. Her father, mother and one sister, aged six years, were living and well.

The girl was born at full term with normal delivery; birth weight was seven pounds. Artificial feeding was started after six weeks. She had pertussis in December 1938 and chickenpox in April 1939. No residuals were apparent from either illness.

Upon admission physical examination revealed a poorly nourished white female apparently suffering with abdominal distress. Temperature was 99.4° F. (rectal).

The pulse and respirations were not recorded. The weight was 22 pounds. There was moderate pallor of the skin and mucous membranes, prominent bilateral periorbital ecchymosis with moderate right exophthalmos, and a palpable abdominal mass in the upper left abdominal quadrant.

The patient's illness ran a rapidly progressive unfavorable course. She received symptomatic treatment; and she was given deep roentgen-ray therapy over four areas, total 1180 R, which was discontinued at the request of her mother who felt that the treatment was not beneficial. During the first part of August the patient developed a tumor mass in the right infraorbital region, which spread later to the left antrum, roof of the mouth, gum margins and tongue. During the latter part of August she developed transient soft swellings of the neck and submaxillary regions with progressive bilateral exophthalmos. The patient was unable to take nourishment and at the request of the mother fluids were not given. Inanition became marked and the patient died at 2:55 p.m., September 2, 1939.

Laboratory and Roentgenological Findings: The red cell count varied from 3,500,000 with 65 per cent hemoglobin at the time of admission to 1,240,000 with 50 per cent hemoglobin just before death. The white cell count was not increased; the differential counts varied from 50 to 20 per cent lymphocytes, monocytes 2 to 7 per cent, and polymorphonuclear neutrophiles 47 to 80 per cent.

Roentgenograms of ribs, lungs, humeri, femora and proximal half of tibiae and fibulae appeared normal throughout the course. Films of the skull showed suture separation with multiple areas of bone destruction, particularly in the frontoparietal region.

Postmortem Examination. Gross: The body was markedly undernourished and there was marked pallor throughout. Both eyes showed exophthalmos, most marked on the left, with prominent left periorbital ecchymosis. Nodular, soft and necrotic tumor involved the palate, tongue and gum margins, with several upper teeth loose and free in the tumor. There was moderate bilateral cervical adenopathy. No scars or other marks of identification were noted.

A large, soft, hemorrhagic and friable tumor mass was noted almost filling left abdominal cavity. This tumor involved the left suprarenal gland and compressed the left kidney but did not invade it. The mass measured approximately 20 cm. in diameter. Ascites was not present. The tumor was adherent to the omentum, pancreas and parietal peritoneum. The stomach and intestines were normally distended with gas. The liver weighed 345 grams, and the capsule was mottled with grayish-white, irregular, indurated areas of tumor. The organ was firm and upon cut section many scattered, irregular areas of tumor metastasis were noted which appeared yellowish-white in color. The gall-bladder, spleen, right suprarenal, right kidney and remaining genito-urinary organs did not show any significant gross pathologic changes. The mesenteric and abdominal lymph nodes were enlarged and hard, showing gross evidence of tumor metastasis. The gastrointestinal tract, lungs, heart and aorta were not remarkable. Permission was not granted to examine thoroughly the head and neck.

Microscopic Study: Various sections from the tumor mass involving the left suprarenal gland and the metastatic lesions in the liver and lymph nodes showed similar pictures. Large and small irregular masses and clumps of small, round to polygonal cells with little cytoplasm and large hyperchromatic and vesicular nuclei were present which were separated by imperfect strands and trabeculae composed of parallel fibrils. Areas of hemorrhage and necrosis were present. An occasional imperfect rosette formation was noted, and scattered among the small round cells were occasional large round and spindle cells with vesicular nuclei.

In addition to the metastatic sites already mentioned, various sections of the lungs showed the presence of very small foci of tumor cells similar to those found in the main neoplastic mass.

Case 2. R. A. W., male, aged five years, entered W. R. G. Hospital on March 17 and died September 26, 1938. The chief complaints upon admission were loss of weight, weakness, nausea, vomiting, bone pains, and a tumor mass in the right abdomen. The apparent onset of symptoms occurred about September 10, 1937 with cramping epigastric pains. For several weeks prior to this the mother observed that the child would frequently cry out while asleep. During the latter part of September 1937 the patient developed pain in the extremities, particularly in the right arm and left thigh. A progressive pallor developed, and in January 1938 a tumor mass was felt in the abdomen to the right of the umbilicus, without ascites, together with a bilateral cervical and postauricular lymphadenopathy and a nodular swelling over the right frontal region. According to the mother the patient ran a fever ranging from 99 to 102° F. for from 7 to 10 days alternating with afebrile periods of from 3 to 12 days.

The family history and past history were not pertinent.

Upon admission physical examination revealed an emaciated white male about the stated age, appearing in extremis. Temperature was 104° F., pulse 104, and respirations 24. Length was 44 inches and weight 34 pounds. The skin was pale yellow and waxy. The lymph glands of the neck, axillae and groin were enlarged and hard. A tumor mass about 10 cm. in diameter was palpated in the right abdomen. There was wasting of the muscles of both thighs. Blood pressure was 94 mm. Hg systolic and 78 mm. diastolic. The lungs and heart were not remarkable.

The progress of the patient in the hospital was progressively downward. He received symptomatic treatment with deep irradiation over several areas, totalling 14,500 R up until date of death. Following irradiation the tumor masses decreased in size markedly. The patient failed progressively and died on September 26, 1938 at 6:30 a.m.

Laboratory and roentgenological findings: The red cell count varied from 2,800,000 with 55 per cent hemoglobin upon admission to 1,500,000 with 25 per cent hemoglobin before death. The total leukocyte count dropped as low as 100 with definite lymphocytic preponderance. Urine examinations were not remarkable.

Numerous roentgenograms showed scattered areas of rarefaction in all the long bones and in the skull. Following irradiation some recalcification occurred in many areas.

A biopsy of a cervical lymph gland on March 19, 1938 confirmed the clinical diagnosis of neuroblastoma.

Postmortem Examination. Gross: The body was markedly emaciated and showed prominent pallor. There was moderate exophthalmos of the right eye with surrounding soft tissue ecchymosis. There was definite generalized lymphadenopathy.

The right suprarenal gland was involved in a tumor mass measuring 3 by 1.5 by 1.4 cm., after much irradiation. This tumor was soft, friable and hemorrhagic. The left suprarenal and kidneys were not involved. The mesenteric and abdominal lymph nodes were large and showed gross tumor metastasis. The liver was large, weighing 675 grams. Numerous pale yellowish-red metastatic foci were present on the capsular surface as well as in the parenchyma. The gall-bladder and spleen were not remarkable. Both testes were large, nodular and on cut section showed the organs to be replaced by tumor. Metastatic foci, nodular in character, were noted on the pleural surfaces, and in the lung parenchyma were many scattered, ill defined areas of hemorrhagic infiltration varying from 1 to 4 cm. in diameter. In the centers of these areas a paler, pink translucent tissue was seen. About 125 c.c. of thin, sanguinous fluid were noted in the pericardial sac and scattered small hemorrhagic foci were noted on the epicardium. These foci did not involve the myocardium. The heart weighed 135 grams. The aorta was not remarkable.

The distal end of the right femur, beginning approximately 15 cm. above the articular surface, showed a gradual enlargement of the bone with aplasia of the bone marrow. Permission was not granted for examination of the skull and contents.

Microscopic Study: The tumor was composed of masses of hyperchromatic polygonal cells, sometimes assuming a spindle shape, having large, densely stained nuclei and scanty cytoplasm. These masses were surrounded by rather dense fibrillated stroma. Occasionally they appeared to form incomplete acini but nothing that could be designated a rosette was seen. All metastatic lesions showed a similar histologic picture.

Case 3. H. A. M., male, aged 18 years, was admitted to the hospital on July 17 and died on November 10, 1936. The chief complaints upon admission were pain and tenderness in the lower right quadrant, nausea and vomiting. Temperature was recorded at 99.2° F., and the total leukocyte count was 12,500 with 69 per cent polymorphonuclear leukocytes. A diagnosis of appendicitis was made, and the appendix was removed but showed no remarkable pathologic changes. The patient's condition did not improve after operation and on September 8, 1936 a large, moderately firm and tender tumor mass was noticed filling the entire upper right abdominal quadrant to the midline and down to the umbilicus. The history and physical examination indicated a subphrenic or liver abscess and on September 14, 1936 the abdomen was again opened, at which time a large tumor mass was noted which was retroperitoneal and involved the right lobe of the liver.

The family and past history were not pertinent.

The course of the patient in the hospital was progressively downward. Emaciation developed steadily as did a secondary anemia. The operative wound drained freely and frequent dressings per day were applied. Fever from 99° to 102° F. persisted. Examination of the heart and lungs showed no pathologic changes. The tumor mass in the abdomen became progressively larger. The treatment was purely symptomatic. The patient became weaker each day and died on November 10, 1936 at 3:30 a.m.

Laboratory and roentgenological findings: Urine and feces examinations were repeatedly within normal limits. Blood counts constantly showed an average leukocyte count of about 12,000 with 69 per cent polymorphonuclear leukocytes. There was also a progressive "shift to the left." The red cell count dropped to 1,300,000 with 38 per cent hemoglobin. Various blood chemistry examinations and repeated Wassermann and Kahn reactions were all negative.

Numerous roentgenograms of the bones of the body were all negative. Plates on October 17, 1936 showed the right leaf of the diaphragm to be extremely high, the right lung compressed, and marked pleural thickening along the lower half of the chest in the axillary line. No deep irradiation was given.

Postmortem Examination: The body was markedly emaciated, with a length of 62 inches and estimated weight of 55 pounds. The upper right half of the abdomen was distended and the right side of chest became bulged owing to prominent flaring of the ribs. A longitudinal, recent surgical incision about six inches in length was present in the right hypochondrium.

In the right retroperitoneal space a large, soft, friable and hemorrhagic tumor mass about the size of a man's head was noted which was adherent to and continuous with the right lobe of the liver. This mass compressed the right kidney and pushed all abdominal structures to the left. Traces of suprarenal gland were noted at the upper pole of the right kidney, the greater portion of the gland being replaced by tumor. Ascites was not present. Small nodules of tumor metastasis were noted on the parietal peritoneum and two small nodules were noted in the lower lobe of the left lung.

All other viscera, together with all bones, were essentially normal.

Microscopic Study: Sections of tumor showed masses and islands of small and irregular cells with very little cytoplasm and with large, hyperchromatic nuclei. These masses were partially set off and trabeculated by longitudinal groups of thin fibrils. An occasional rosette was noted. The tumor was quite vascular and scattered areas of hemorrhage were present along with scattered areas of necrosis.

Conclusions

1. Neuroblastoma of the suprarenal medulla is a definite pathologic entity and is relatively rare. About 220 cases have been reported in the literature; three additional cases of our own are added.

2. Too much emphasis has been placed upon the so-called clinical syndromes of Pepper and Hutchinson. The histologic picture of each type is identical, and from a survey of the cases reported there is much overlapping of the criteria. In about 20 per cent of the cases a definite classification is impossible.

3. Sex is not a factor in the incidence of these tumors and in general, the younger the patient, the more undifferentiated are the tumor cells and the greater is the degree of malignancy.

4. The symptoms depend entirely on the position, size and extent of the primary tumor, together with the location of the metastases. The usual clinical course is progressive with rapidly fatal termination.

5. The tumor is sensitive to irradiation, contrary to general opinion, and this treatment prolongs the course of the case. Although one case is reported in the literature as well 15 years after surgical removal of the suprarenal tumor, it is generally concluded that surgery is not of benefit.

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CASE REPORTS

HEMOPHILUS INFLUENZAE BACTEREMIA: REPORT OF TWO CASES RECOVERING FOLLOWING SULFATHIAZOLE AND SULFAPYRIDINE*

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Recently we have observed two patients with *Hemophilus influenzae* bacteremia who recovered following chemotherapy. One patient had pneumonia and the other had a primary lesion in the biliary passages. Since *H. influenzae* infection of the bile passages was unique in our experience, we were stimulated to review the subject of *H. influenzae* bacteremia in general as well as to report our recent experience.

Case Reports

Case 1. A young man with lobar pneumonia, H. influenzae *in the sputum and circulating blood, recovers promptly following sulfapyridine.*

A white man, 30 years of age, was admitted to hospital complaining of fever, cough, and pain in the chest which was exaggerated by respiratory effort. Aside from the fact that he had had a head cold and a slight cough for two weeks before his acute illness, he had been well. Twenty-four hours before admission he had a chill which was followed by high fever, increasing cough, bloody sputum, and pain in the right chest.

On examination, the temperature was 103° F., the pulse rate 120 per minute, and the respirations 30 per minute. Moderate cyanosis was present and there were signs of pneumonia over the right middle and upper lobes.

The laboratory examinations showed a leukocytosis of 23,400 per cubic millimeter. There were many *H. influenzae* in the sputum but no pneumococci. The roentgen-ray examination of the chest confirmed the diagnosis of pneumonia and the blood culture was positive for *H. influenzae.*

The course of the illness is shown in figure 1. Following the use of sulfapyridine, the blood was cleared of organisms and the temperature gradually declined to normal. There were no complications.

This case, then, is an example of *H. influenzae* pneumonia following an upper respiratory infection in which there was consolidation of two lobes of the right lung and bacteremia. Recovery without complications followed treatment with sulfapyridine.

H. influenzae infections of the lungs are more often secondary to some other infection, such as influenza virus infection, or they occur as mixed infections of the lung. They may be isolated from the sputum of patients with lung abscess, bronchiectasis, or other chronic infections of the lung, and occasionally they are secondary invaders in tumors of the lung. Occasionally they cause pneumonia

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without preceding infection. These infections played a prominent part in some of the cases of pneumonia following the pandemic of influenza in 1918 and, indeed, by some students of the pandemic they were considered to be responsible for the epidemic itself. That these organisms may cause serious infections there is no doubt. Whether the experience in this isolated case of pneumonia will be confirmed in others with the same infection and bacteremia following sulfapyridine, only time will tell.

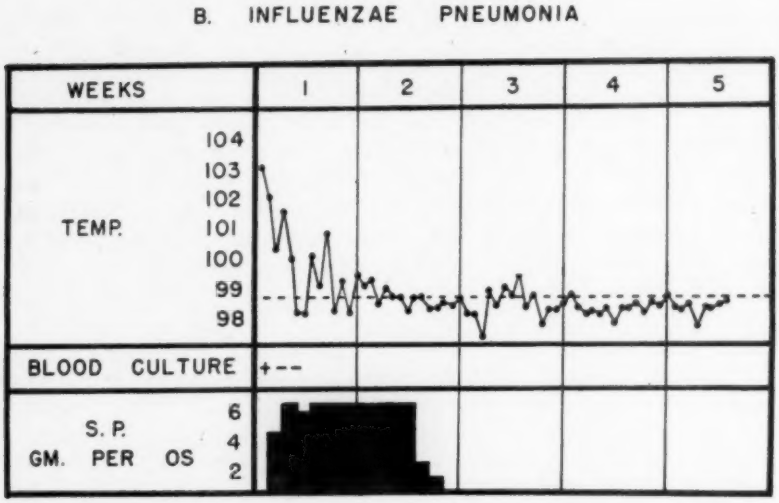

FIG. 1.

S. P. = Sulfapyridine.

Case 2. A young man has repeated attacks of biliary colic with jaundice; then chills, fever, jaundice, hepatomegaly, splenomegaly, H. influenzae *bacteremia. The blood was temporarily sterilized by sulfathiazole. Complete recovery followed cholecystectomy and drainage of common bile duct.*

A 34 year old, white chef entered the Evans Memorial March 21, 1940, complaining of recurrent jaundice associated with mid-epigastric pain, chills, fever and vomiting. His present illness began about two years before at which time he began to have frequent nocturnal attacks of indigestion, which were characterized by sharp, colicky, mid-epigastric pain, which did not radiate. The following day, the urine would be dark brown in color. One year previous to entry he had a sudden onset of jaundice associated with mid-epigastric and right-sided pain of three weeks' duration. He finally recovered from this attack. His immediate present illness began nine days before we saw him, and it was characterized by gradually deepening jaundice, intermittent chills and fever, dark urine, and light-colored stools. He had had an attack of pneumonia with pleurisy at the age of seventeen. He had always been overweight and at the age of 26 he weighed 238 pounds. Two weeks before entry to this hospital he weighed 195 pounds.

On admission, the general physical examination revealed a well-developed and well-nourished man who was deeply jaundiced, but in no apparent distress. The temperature was 99°. The skin and mucous membranes were yellow. There were several telangiectatic spots over the nose and back of the hands. The skin was warm and dry, and there were many excoriations over the upper arms, abdomen and thighs,

which resulted from excessive scratching. The heart and lungs were clear. Blood pressure was 126 mm. Hg systolic and 72 mm. diastolic. The abdomen was well developed and symmetrical. There was definite tenderness just to the right of the mid-epigastrium. The spleen was easily palpable four fingers' breadth below the costal margin. The liver was felt about six centimeters below the costal margin, was smooth in outline and moderately tender. Gall-bladder was not felt. Genitalia were normal. Rectal examination was negative. There was a scar of an old varicose vein with considerable pigmentation over the inner aspect of the lower half of the left leg; otherwise, the extremities were normal.

The essential laboratory data were as follows: The urine showed albumin, bilirubin, and urobilinogen. With the exception of a leukocytosis of 18,700 the blood

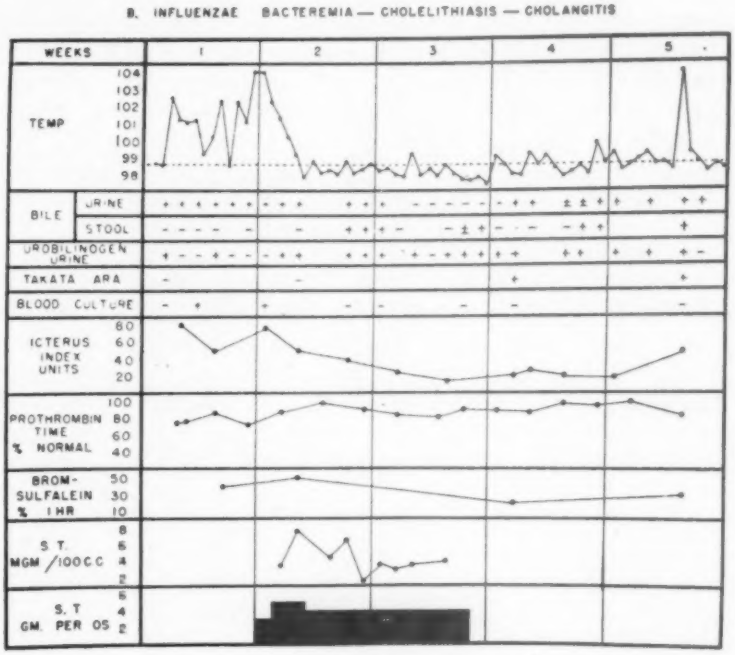

FIG. 2.

S. T. = Sulfathiazole.

was normal. The icterus index was increased to 80 units. The stools contained bile pigment irregularly. The other laboratory examinations are shown in figure 2.

By roentgen-ray examination a flat film of the abdomen showed no evidence of a calculus in the gall-bladder. The intravenous Graham test revealed poor concentration of the dye in the gall-bladder, but there was no definite evidence of stone.

The course of the patient's illness is shown in figure 2. During the first 10 days there was high, irregular fever. The urine contained bile pigment and urobilinogen, and the icterus index was elevated. The prothrombin time was slightly reduced and the bromsulphalein test showed a decreased excretion of the dye. When it was learned that he had an *H. influenzae* bacteremia, sulfathiazole was given by mouth, in amounts averaging four grams a day. Following this treatment the temperature returned to normal, and the patient showed temporary improvement. There was a recurrence of the fever and jaundice so that an operation was advised. Dr. Howard Clute operated

and found a cholecystitis and cholelithiasis with stones in the common duct and cholangitis. Following operation he made a satisfactory recovery and has remained well.

In the present case, the outstanding features were the recurrent attacks of biliary colic with jaundice; chills and fever with leukocytosis; enlargement of the liver and spleen; bacteremia due to *Hemophilus influenzae* which could not be typed; sterilization of the blood following the exhibition of sulfathiazole; complete recovery following cholecystectomy with drainage of the common bile duct and removal of stones.

In our experience, the isolation of *H. influenzae* from the circulating blood in patients with cholangitis and cholelithiasis was unique. Upon looking into the matter, however, we found that Ophüls [1] had described multiple liver abscesses which were owing to organisms like the influenza bacillus and which were secondary to an infection of the rectum, but we have been unable to find cases of cholangitis secondary to stones resulting from influenza bacillus infection. In view of the fact that these organisms occur so seldom in infections of the liver, the features of *H. influenzae* infection and bacteremia in general are reviewed.

Review of *H. Influenzae* Infection

The *Hemophilus influenzae* bacillus is frequently found in the throat of normal individuals. Once it leaves this habitat it may invade the meninges, the lungs, the circulating blood, the joints, the endocardium, or the kidneys. Indeed, localized infections of various organs of the body, including the throat, liver, or genital organs, have been described. Since several of these infections are of importance they require special comment.

Meningitis. Meningitis caused by the *Hemophilus influenzae* is accompanied by bacteremia in 70 per cent of cases when the blood is cultured early in the course of the disease. Most of the cases occur in children under the age of three years and the fatality rate following serum and chemotherapy has been greatly reduced.[2] The organisms causing this infection almost always are Type B bacilli. If the patient lives long enough to develop metastases they are usually in the joints, and the involvement is generally polyarticular rather than monarticular.

Arthritis. Many of the cases of *H. influenzae* arthritis have been reviewed by Weaver and Sherwood [3] who divided the cases into two groups: (1) those associated with meningitis and (2) those with arthritis alone. They stress the fact that most of the patients are under two years of age although one of their patients was 59 years of age, and other cases have been reported in adults. In the cases of arthritis following meningitis the outcome was usually fatal and the arthritis was a polyarthritis. In the cases without meningitis, recovery was the rule and the arthritis was more likely to be monarticular. In a few cases of arthritis caused by this organism, the original process was in the bone and the infection spread to involve the joints as a secondary process.

Endocarditis. It has long since been recognized that the influenza bacillus is one of the infecting organisms in subacute bacterial endocarditis.[4, 5, 6] There is nothing peculiar or characteristic about the bacterial endocarditis caused by this organism since renal complications, mycotic aneurysms, and the other fea-

tures of infective endocarditis may also be observed in influenza bacillus infections.[4,5,6]

Kidney Lesions. Aside from the cases of focal embolic glomerular nephritis owing to the influenza bacillus, Albright, Dienes and Sulkowitch [7] have described cases of pyelonephritis with nephro-calcinosis caused by *Hemophilus influenzae* which were relieved by sulfanilamide. The calcium deposits in the kidney were disclosed by roentgen-ray examination and they were unequal in size and much larger than the calcium deposits which are seen in hyperparathyroidism. The urine in these cases is alkaline and, as long as the infection persists, it remains so. Other reports of infections of the kidney by this group of organisms have been made by Burkland and Leadbetter,[8] Davis,[9] and Wright.[10]

Throat Infections. Influenzae bacillus bacteremia following infections of the throat have been described by Frank,[11] Koch,[12] Lemierre, Meyer and Laplane,[13] and Hotz.[14] In the case described by Frank, a 19-year-old boy developed *H. influenzae* bacteremia following a bilateral tonsillitis with retrotonsillar abscess, thrombosis of the maxillary and internal jugular vein, and metastatic abscesses in the lungs and pleura. This was a typical case of posttonsillitis thrombophlebitis which made its appearance seven days after the primary illness had apparently subsided.

In the first case described by Lemierre, Meyer and Laplane [13] there was an ulcerative pharyngitis, bronchopneumonia, bullous lesions of the neck, and arthritis of the sternoclavicular joint. Influenza bacilli were isolated from the blood, the throat, and the bullous lesion of the skin. He considered this case to be one of posttonsillitis sepsis. It is plain, then, that the influenza bacillus is one of the organisms which can cause thrombophlebitis of the deep cervical veins and bacteremia with multiple abscesses.

Of considerable interest are the cases of influenza bacillus pericarditis which begin as a sore throat and signs of laryngeal stenosis. Hotz [14] described such a case and collected others from the literature. In brief, the illness begins with a catarrhal sore throat which is soon followed by acute inflammation of the larynx with symptoms and signs of stenosis. These signs may disappear with only slight improvement in the general condition of the patient. Then signs of pulmonary, pericardial, or mediastinal infection follow. It is quite possible that the influenza bacillus is a secondary invader in these cases, since acute inflammatory lesions of the larynx with stenosis are not infrequent in children without influenzal infection.

Puerperal Sepsis. Occasional cases of puerperal sepsis have been reported as a result of infection with the influenza bacillus [15, 16] and local infections of Bartholin's glands [17] or of the Fallopian tubes have been reported. Nye [18] has isolated *Hemophilus influenzae*-like bacilli from the normal cervix and vagina and from the circulating blood of patients with puerperal sepsis so that there seems to be no doubt that these organisms, which can also be found in the stools of some patients, may cause puerperal sepsis in some cases.

Infection of the Conjunctivae. Leichtentritt and Schober [19] described a case of *H. influenzae* bacteremia associated with a relapsing skin eruption, parotitis, and arthritis. The patient was a four year old child who developed a bilateral conjunctivitis which was followed within eight days by high irregular fever and a skin eruption over the face and extremities, maculo-papular urticaria in type.

H. influenzae were isolated from the circulating blood on three occasions. The patient recovered after an illness of six weeks' duration.

Influenza Bacillus-Like Organisms from the Appendix. Hudacsek and Kerbler [20] have recorded the isolation of influenza bacilli from the appendices of patients with appendicitis and from peri-appendiceal abscesses. This paper stresses the fact that these organisms occur in the gastrointestinal tract and it is possible that invasion of the biliary tract, the liver, or the genitourinary tract may occur from this source.

Comment

From this discussion of *Hemophilus influenzae* bacteremia, it would seem clear that these organisms may enter the circulating blood from the nasopharynx, the lungs, the meninges, or the bile passages. They may be found in the nose and throat, the gastrointestinal tract, and in the vagina of normal individuals. Once bacteremia is established, metastatic foci of infection may be set up in the joints, endocardium, or kidney.

Local infections have been described in the meninges, endocardium, throat, lungs, pericardium, kidney, liver, the rectum and genital tract in men and women.

Bacteremia associated with meningitis is frequently a fatal disease. There is recent evidence, however, to suggest that intensive treatment with rabbit serum and sulfanilamide will reduce the fatality rate in this disease especially in children over three years of age.[2]

Bacteremia associated with arthritis without meningitis has a good prognosis, largely because the infection tends to focalize in the joints where drainage of the focus of infection can be done effectively.[3]

The renal infections due to this organism respond favorably to sulfanilamide.

In any case of *H. influenzae* bacteremia, then, sulfathiazole should be used at once. If meningitis is present, it is perhaps well to use sulfanilamide or sulfapyridine since these drugs are found in the meninges in much higher concentration than sulfathiazole. In addition to chemotherapy, intensive intravenous serum treatment should be used.

We have reported two cases of *H. influenzae* bacteremia which recovered following chemotherapy. In one the original focus of infection was the lungs and, in the other, it was the biliary tract.

A brief review of *H. influenzae* bacteremia is presented.

Since this paper was written, Sinclair's report [21] of *H. influenzae* type B in acute laryngitis with bacteremia has appeared. The organisms were isolated from the blood in all cases and four out of ten patients died. Half of the children were over five years of age. The disease was characterized by an acute onset with fever, leukocytosis, the history of a severe sore throat, the evidence of laryngitis, and the signs of "shock" due to the infection and the laryngeal obstruction. Tracheotomy, sulfonamide and specific serum therapy are all important therapeutic measures.

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BRUCELLA ENDOCARDITIS OF CONGENITAL BICUSPID AORTIC VALVE*

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A review of cases of brucellosis with endocarditis recently was reported by Smith and Curtis.[1] This entity, despite the prevalence of undulant fever in this country, seems still to be a rarity. Of the 10 cases reported, only five [1, 3] have occurred in the United States. The present case is reported because of its rarity and also because it is the first recorded to have been superimposed on a congenital valvular lesion. In addition the pathological changes in the other viscera are of interest.

CASE REPORT

C. W., aged 28, white male, was admitted to the Lenox Hill Hospital on February 24, 1940. He was born in Germany but left there at the age of 10 for South America where he stayed seven years. In 1929 he came to the United States and worked on a farm until his present admission. In 1928 he had chest pain, dyspnea and a productive cough for one month and was said to have had a "heart attack." Since 1928 he had had slight dyspnea on moderate exertion but no other symptoms of loss of cardiac reserve.

His present illness began in December 1939 when he developed a sore throat, dizziness, weakness and frequency of urination. He was seen by a physician and told he had kidney trouble. He improved in three weeks' time. In late January 1940 he developed another sore throat, associated with chills, fever and anasarca. Oliguria and frequency of urination were present. In one week's time the edema subsided but the chills and fever persisted. His dyspnea, however, became more pronounced.

On admission to the Lenox Hill Hospital his temperature was 104° F., respirations 28, pulse 90. He appeared acutely and chronically ill, was moderately dyspneic and orthopneic. There was no evidence of jaundice, cyanosis or petechiae.

The eyes showed slight puffiness of the lower lids. The tonsils were prominent and cryptic, the pharynx was granular and injected, the uvula was bifid. Examination of the neck showed marked arterial pulsation. The lungs showed no abnormal findings.

The heart was enlarged to the anterior axillary line in the fifth intercostal space. Systolic thrills were palpable at both base and apex. A precordial heave was present. At the apex there was audible a harsh systolic blow which was transmitted to the axilla and was followed by a short, soft blowing diastolic murmur. At the base also loud systolic and diastolic murmurs were heard. An inconstant to and fro pericardial friction rub was present. The rhythm was regular. The blood pressure was 105 mm. Hg systolic and 80 mm. diastolic.

The abdomen was soft and relaxed. The liver was enlarged to three fingers' breadth below the costal margin and the spleen to two fingers' breadth. The latter was moderately tender. Slight clubbing of the finger nail beds was present, and a one plus pitting edema of the pretibial region was found. The genitalia were normal.

Admission Laboratory Data: Hemoglobin 66 per cent, red blood cells 4.05 million, white blood cells 9,300 with 58 per cent neutrophiles, 40 per cent lymphocytes and 2 per cent monocytes. Urine: Specific gravity 1.020; albumin 4 plus; glucose negative;

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From the Medical Service of Dr. Otto M. Schwerdtfeger, Lenox Hill Hospital.

acetone one plus. Microscopically 10 to 15 red blood cells, 5 to 8 white blood cells and numerous hyalin casts per high power field were found.

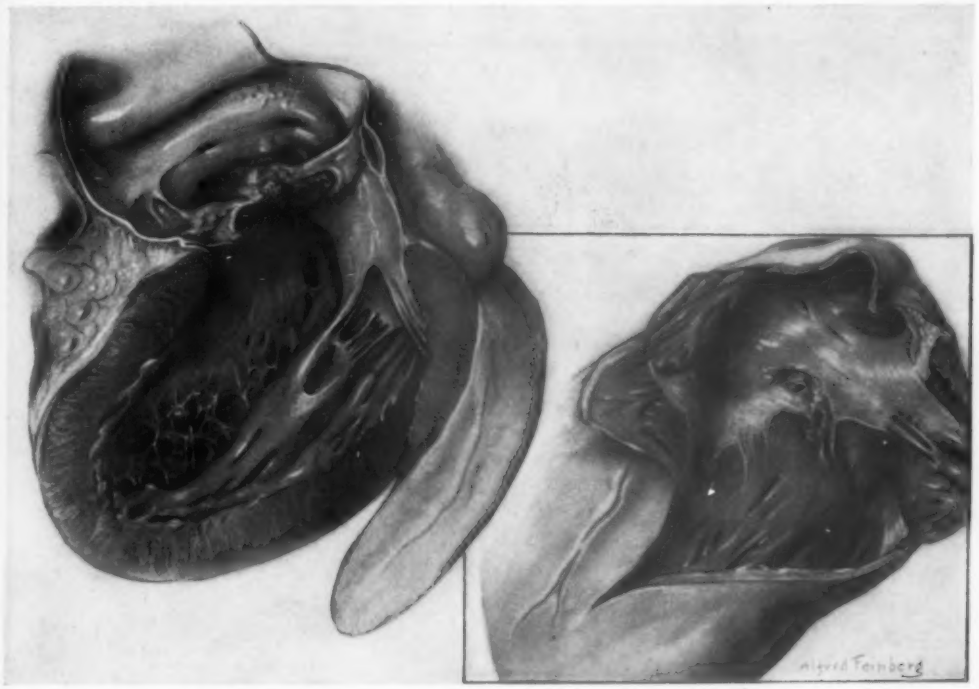
Blood Chemistry: Urea 41.6 mg. per cent; creatinine 3.2 mg. per cent; uric acid 4.8 mg. per cent; glucose 81 mg. per cent; CO_2 combining power 35.7 volumes per cent.

The stool examination was negative for blood.

Erythrocyte sedimentation rate was 22 mm. in 15 minutes (normal 5 mm.).

Blood Wassermann test was negative.

Course: The patient was in an extremely toxic condition. Repeated blood cultures taken on routine agar media showed no growth. Ten days after admission an agglutination for *B. melitensis* was reported positive in dilutions as high as 1 to 500.



A *B*

FIG. 1. Drawings of (*a*) Left heart showing vegetation on bicuspid aortic valve with perforation. Note rolled edges of valve. (*b*) Right heart showing exit of perforating tract above tricuspid leaflet.

He continued to have chills and fever up to 104° F. Two weeks after admission, tenderness of the nail beds was noticed for the first time, and shortly thereafter innumerable petechiae were present over the entire body including the fundi and oral passages. Stool examinations now gave a positive benzidine reaction. Blood cultures taken in a carbon dioxide atmosphere were reported positive for *Brucella abortus* and the opsonocytophagic reaction was markedly positive. All intradermal allergenic tests, however, were negative. Electrocardiographs showed left axis deviation, regular sinus rhythm and a PR interval varying between 0.19 and 0.23 second. A teleroentgenogram showed marked generalized cardiac enlargement but no typical contour.

The patient's condition became progressively worse. The blood urea fluctuated between 39 and 71 mg. per cent. The specific gravity of the urine during the last

three weeks remained fixed at 1.012. Albuminuria and hematuria were constantly present. No granular casts were ever found. During his course the patient received four transfusions of whole blood. He died suddenly on the thirty-sixth day of hospitalization.

Necropsy Findings: Autopsy was performed six hours after death. The external features were similar to those described clinically.

The heart (figure 1) weighed 620 grams and lay free in the pericardial sac. There was no effusion or evidence of pericarditis. Enlargement externally was mainly left ventricular. When the right auricle was opened the endocardium was found to be smooth and glistening except for a small area just above the anterior cusp of the tricuspid valve where two small perforations were visible. The perforations had

FIG. 2. Photomicrograph of a section of the raphe of the anomalous valve (× 15). Weigert's elastic tissue stain.

friable necrotic edges. The tricuspid valve orifice admitted three fingers and was otherwise normal. The right ventricle and pulmonary valve were not unusual. The left auricle was normal in size and the endocardium smooth and delicate throughout. The orifice of the mitral valve admitted two fingers. The valve leaflets were very thin and delicate as were the chordae tendineae. The left ventricle was markedly hypertrophied and dilated, the wall measuring 2.6 cm. at its thickest part. The aortic valve presented only two cusps, the larger of the two being incompletely divided by a raphe. The width of the larger cusp was smaller than the sum of two normal cusps. A large friable grayish red vegetation measuring 3.5 by 3 cm. partially involved both cusps including the commissure between them. A sinus tract originating in this ulcerative vegetation penetrated through the smaller cusp into the sinus of Valsalva, thence through the base of the aorta and terminated in the right auricle as the perforations described above. The free edges of the aortic cusps were rolled and thickened. The coronary ostia, one arising from behind each cusp, were widely patent as were the coronary arteries. The aorta was otherwise normal except for small atheromata.

The lungs showed merely congestion and edema especially at the bases and posteriorly.

The liver weighed 2660 grams, was deep purplish red in color and extended three fingers' breadth below the costal margin.

The spleen weighed 630 grams, was firm in consistency and extended two fingers' breadth below the costal margin. Three pinkish yellow triangular areas of infarction, the largest measuring three cm. at the base, were present. On section the appearance of infarction was confirmed. In other areas the Malpighian corpuscles were prominent in an otherwise congested pulp.

The adrenals were not unusual.

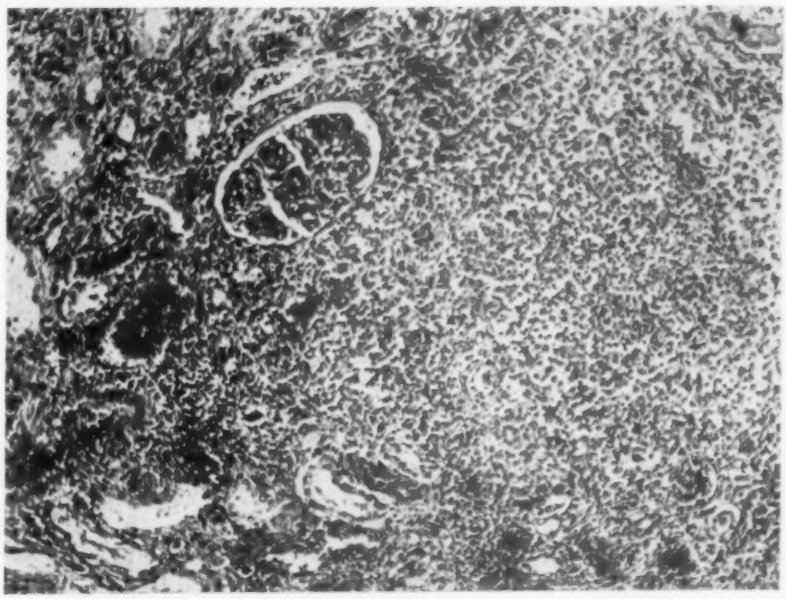


FIG. 3. Photomicrograph of abscess in interstitial tissue of kidney (×75). Note normal glomerulus.

The kidneys weighed 360 and 330 grams respectively. The capsules were tense and stripped with slight difficulty. The denuded surface revealed pin-point yellow spots over its entire extent. The demarcation between cortex and medulla was indistinct and the cut surface presented an edematous appearance. The calyces and pelves were normal.

The gastrointestinal tract was not unusual.

Permission for examination of the head was not obtained.

Microscopic Examination: Heart: In the region of the perforation necrosis and acute inflammatory reaction were evident. This reaction was also present on the aortic valve superimposed on which was the vegetation, granular and bluish, and hyalinized in areas with deeply staining areas intermingled between the eosinophilic staining parts. Section of the aorta in the region of the raphe (figure 2) dividing the anomalous valve showed the usual three layers to be present. The endocardium continued uninterrupted over the raphe. The elastic tissue of the media became thinned out as the raphe was approached. The raphe itself consisted of dense hyalin material. The adventitia was not unusual. There was no evidence of any inflam-

matory process either in the form of cellular or vascular reaction. The myocardium showed muscle fiber hypertrophy. There was no evidence of rheumatic involvement.

Congestion and edema were present in the lung sections. In addition were seen conglomerate areas of plasma, round and polymorphonuclear cell infiltration in some of which clear eosinophilic material gave the appearance of necrosis.

The architecture of the liver was well preserved. The central veins and sinusoids were markedly congested with surrounding compression of liver cells.

Sections of the spleen showed the areas of infarction to be well demarcated. The remainder of the splenic tissue showed evidence of acute splenitis and congestion with focal areas of necrosis and cellular infiltrations as were seen in the lung sections.

Kidneys: The main changes were in the interstitial tissue in which areas of polymorphonuclear and round cell infiltration with necrosis were prominent (figure 3). Edema also was present. Scattered glomeruli were atrophic and occasional ones completely degenerate. No endothelial proliferation or crescents were seen. The tubules showed parenchymatous swelling and frequently were filled with clear staining material and occasionally red cells.

Pancreas and adrenals were not unusual.

Comment

The infrequency of *B. melitensis* endocarditis has been referred to. The present case is the sixth to be recorded in this country. All except that reported by de la Chapelle have occurred in rheumatic or sclerotic valves. The only finding in his case was a thickened aortic cusp. Our case is the first to be superimposed upon a congenital lesion.

Difficulty in diagnosis may well be a reason for this apparent rarity. All blood cultures taken on routine agar media showed no growth. The first taken in a CO_2 atmosphere showed growth. The diagnosis, however, was entertained after a serum agglutination was done because of the patient's occupation. Skin tests repeated several times were all negative. Opsonocytophagic reaction was markedly positive.[4] For these reasons it is pointed out that in cases of bacterial endocarditis yielding negative blood cultures on routine media the other diagnostic procedures referred to above be resorted to especially if occupation or pastime suggests the possibility of *B. melitensis* infection.

During the course of this patient's disease it was suggested by one of us that there might be an underlying congenital lesion such as a bicuspid valve. Prolongation of the PR interval has been recorded on numerous occasions[5, 6, 7] in cases in which bicuspid aortic valve was found at necropsy. The authors have seen one such previous case in which no other pathological abnormality was present either clinically or at necropsy. We realize, however, that this may be coincidental owing to toxic influence on the vagus nerve.

The fact that the patient was told he had heart disease in 1928 is likewise of interest. It would seem that this patient did not have *B. melitensis* endocarditis for 12 years. The only apparent explanation seems to be that he may have had murmurs, especially at the base, arising from a thickening of the aortic cusps resulting from mechanical wear and tear of congenitally imperfect cusps.

The necropsy findings in other viscera of this patient are comparable to those pointed out by de la Chapelle although probably of a more extensive nature. These were possibly on a septicemic basis. Urinary findings ante mortem were not typically those of glomerular nephritis though this was suspected; post

mortem the glomeruli were for the most part spared. Diffuse abscesses have been found in a few cases of undulant fever. The majority show no pathologic changes of the kidney.

Treatment of *B. melitensis* endocarditis has not been a topic of discussion by most authors probably because of its rarity. When mentioned it is in relation to undulant fever in general. In the present instance supportive treatment with blood transfusion was given. Chemotherapy was avoided early because of obvious renal damage and anemia. Later when the diagnosis of endocarditis was confirmed the course was of such short duration that he died before institution of chemotherapy.

SUMMARY

A unique case of *B. melitensis* endocarditis superimposed upon a congenital bicuspid aortic valve is reported. The importance of the various diagnostic procedures is discussed stressing the use of the opsonocytophagic and serum agglutination tests, and also the use of the CO_2 atmosphere in the isolation of *Brucella abortus* from the blood. The abscess formation in the various viscera and especially in the kidney is pointed out in view of the fact the *Brucella abortus* is usually not considered a pyogenic organism.

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INFECTIOUS MONONUCLEOSIS AND ENCEPHALOMYELITIS*

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ONE of the least frequent complications of infectious mononucleosis is involvement of the central nervous system. Because of the fact that a rather careful survey of the literature failed to reveal any case of infectious mononucleosis associated with evidence of diffuse lower motor neurone disease, the following case is herewith reported.

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From the Department of Medicine, Israel-Zion Hospital.

Case Report

History. E. N., a young male of 21 years, was admitted to the hospital on January 11, 1940, with a story that he had been taken ill three weeks previously with headache, weakness and fever as high as 103° F. He continued working for about a week but finally on December 28, 1939, went to bed with what appeared to be influenza. During the ensuing week he had pain in the back, general muscular weakness, pain in the inguinal regions, and fever. He was, however, up and about part of the time. By January 6 the weakness of muscles had become very marked and the patient became quite irritable, which was not his usual behavior. On the day before admission, on awakening, the patient found that he was unable to move either his hands or feet. On several occasions irregular twitchings, lasting a few seconds and involving the shoulders, were noted by his mother. He had vomited several times prior to admission as well as on the night of admission. Nothing was noted in the boy's past personal history except that he had had measles, scarlet fever, diphtheria and pneumonia as a child and that he had been operated upon for an undescended testicle 11 years previously. The family history was totally irrelevant.

Physical Examination. The patient, a young male of 21 years, appeared acutely ill. Color was fair. Pupils were equal, reacted equally well to light and accommodation. There was a ptosis of the right upper eyelid. Episcleritis of the left eye was present. The fundi were negative. The nose was negative and there were no points of sinus tenderness. The throat showed several hemorrhagic spots. The tongue deviated somewhat to the left. There was a left peripheral facial paralysis. There were some small glands in the left posterior cervical chain and one large gland in the left submaxillary region. There was slight nuchal rigidity. The lungs were negative. The apex impulse of the heart was felt in the fifth interspace in the nipple line. There was no enlargement to the right or left; the aorta was not widened. The sounds were of good quality, regular in rhythm, of normal rate; there were no accentuations. A soft systolic murmur was audible over the mitral area but it was not transmitted. There was no precordial thrill. The systolic pressure was 146 mm. Hg and the diastolic, 80 mm. Hg. Small axillary glands were palpated bilaterally. The liver dullness extended from the fifth rib to one finger's breadth below the costal margin, although the edge could not be felt. Spleen and kidneys were not palpable. A small umbilical hernia was present. Small inguinal glands were present on the right side, and on deep palpation some small glands in the right lower quadrant of the abdomen could be felt. Dermatographia was present. There was an almost complete flaccid paralysis of all four extremities. The patient was able to move only his fingers and toes. There were fibrillary twitchings of his right arm. No atrophy was noted. All deep reflexes were abolished. There was no disturbance of sensation. The right lower abdominal reflex was active; the right upper and left lower abdominals revealed just a flicker. The right cremasteric reflex was present, the left absent.

A blood study four days prior to admission to the hospital showed a hemoglobin of 100 per cent, a red cell count of 4,650,000 and a white cell count of 12,200 with a differential count of 22 per cent polymorphonuclears of which 17 per cent were nonsegmented and 5 per cent segmented forms, 13 per cent lymphocytes, 1 per cent eosinophiles and 64 per cent monocytes. The Westergren index was 10. The heterophile agglutination reaction was positive in dilution of 1:1024. The clinical diagnosis was infectious mononucleosis coupled with a lower motor neurone affection.

Hospital Course. On January 13 a spinal tap was performed. The fluid escaped under an increased pressure of 10 mm. of mercury, was clear, and showed four plus albumin, a faint globulin reaction, four cells per cu. mm. which were lymphocytes, and was negative bacteriologically. The colloidal gold curve and Wassermann re-

actions were negative. A blood count on the same date showed 95 per cent hemoglobin, 5,000,000 red cells, 6800 white cells, with 39 per cent polymorphonuclears of which 15 per cent were nonsegmented and 24 per cent segmented forms, 10 per cent lymphocytes, 35 per cent monocytes, and 16 per cent large lymphocytes. The platelets numbered 210,000. The coagulation time was three and one-half minutes and the bleeding time, four minutes. The blood chemistry was completely normal and the blood Wassermann reaction negative. The urine was also negative.

On January 16 the heterophile reaction was positive in a dilution of 1:512. The blood count showed 98 per cent hemoglobin, 5,280,000 red blood cells, 9250 white blood cells with 48 per cent polymorphonuclears of which 3 per cent were nonsegmented and 45 per cent segmented forms, 3 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes and 23 per cent monocytes. During the first two days of hospitalization the patient had difficulty in voiding and had to be catheterized. There was also slight difficulty in swallowing during this period. For the next five days there was difficulty in breathing, the respirations at times being shallow. Pains were rather severe and appeared in various parts of the body but mostly in the back and upper extremities. There were marked tremors over the body and marked perspiration, although the patient was afebrile. Speech was of the drawling and nasal type.

An orthopedic consultation on January 16 revealed an inability to elevate either shoulder. Forearms were held in pronation, with inability to supinate. Flexion of elbows was absent, and extension was very weak. There was active motion in the right wrist. Extension of the fingers was restricted; flexion was complete. Findings in the left upper extremity were similar but more marked. The right lower extremity showed no motion about the hip. There was some power in the quadriceps, none in the hamstrings. The foot was held in equinus position. The left lower extremity showed no power in any of the muscles except for a slight trace of dorsiflexion of the left foot.

By January 21 motor power of the right upper extremity had improved considerably, and that of the left to a lesser extent. Movements of both shoulders were better, especially that of the right. There was less ptosis of the right upper eyelid. The patient's speech improved. He was able to wiggle some of the toes of the left foot, and there was slight motion of the extensor tendons of his right foot. The patient had been irrational at times during the previous five days. The neurological examination at this time revealed evidence of diffuse lower motor neurone disease with atrophy of the muscles of the hands, forearms, arms and lower extremities; a nuclear left facial paralysis, deviation of the tongue to the left, fibrillations, impaired palatal function and abnormal involuntary movements including myoclonic and chorea-athetoid movements. The clinical picture implicated the basal ganglia, brain stem and spinal cord and warranted the designation of disseminated encephalomyelitis, most likely of virus origin.

A spinal tap done on January 23 showed the spinal fluid to be under increased pressure, about 60 drops per minute, clear, positive for albumin and positive for glucose. It showed two cells per cu. mm., was negative bacteriologically, and showed a total protein of 68 mg. per cent with a one plus Nonne-Appelt reaction.

On February 6 the patient had developed sufficient power in his back to lift himself up in bed. The left facial paralysis was still in evidence, as was the ptosis of the right upper eyelid, both conditions being less marked. The abdominal reflexes were not obtainable. There was still marked weakness in both upper extremities, the right being weaker than the left. There was fairly good power in both biceps but no power in the triceps. Trapezius muscles were active, as were the pectoralis major and minor muscles. The serratus anticus was weaker on the right but active on both sides. Pronation and supination were weak in both forearms. There was atrophy of

arm, forearm and hands of both upper limbs. Flexion and extension were weak. The flexors of the wrists were very weak and atrophied as well as the thenar and hypothenar eminences. When the fingers were extended, there was hyperextension at the metacarpo-phalangeal joints and slight flexion at the proximal interphalangeal joints. Both lower extremities were paralyzed. There was slight power in the quadriceps on both sides and also in the extensors of the toes. The feet were in slight equinus position.

By March 6 a considerable change had taken place in the patient's condition. The facial paralysis had practically disappeared. He was able to move around in bed, although he could not turn onto his abdomen without assistance. There was a considerable amount of improvement in the upper extremities. He was able to make a fist and could open his hand almost to normal. He was able to turn on the radio and make fine movements with the fingers of his right hand, such as winding his wrist watch. He was able to write. He complained of some numbness of the fingers of both hands, more on the left. He had also developed considerable motor power in his lower extremities. He was able to flex the right knee about half way, to raise the entire right lower extremity in midair for about one minute, and to flex the left knee to a lesser degree.

On March 12 the heterophile reaction had become negative. On March 16 bilateral horizontal nystagmus was noted. There was still evidence of left nuclear facial palsy. There was no tremor nor were there any uncontrolled movements of the upper extremities. There was greater strength in the back musculature, and the patient was partially able to sit up. Speech was normal. Motor power in all extremities had returned to a remarkable degree, but the left upper and lower extremities still revealed appreciable impairment. Generalized muscular atrophy especially of the interossei of both hands and of the muscles of the calves, was evident. A moderate left foot drop persisted. The right lower abdominal reflex was active, the others sluggish. The right cremasteric reflex was present and the left was barely elicited. All deep reflexes were greatly diminished. There was no ataxia, but there was some overpointing in the finger to nose test of the left hand. There was no Babinski reflex, no ankle clonus, no sensory change.

On March 20 the patient was discharged after having been able to sit up in a chair for the preceding three days. He felt much stronger generally and really had no complaint other than his motor incapacity. Although motor power had been restored in all extremities to a very marked degree, there was still some weakness of the left upper and lower extremities as compared with the right, a difference of about 30 per cent; otherwise, the physical findings were those noted on March 16. A blood count taken on March 22 showed a hemoglobin of 97 per cent with 5,780,000 red blood cells, 6850 white blood cells, and a differential of 50 per cent polymorphonuclears, 2 per cent eosinophiles, 1 per cent basophiles, 40 per cent lymphocytes, and 7 per cent monocytes.

Treatment was essentially supportive, coupled with the use of thiamin chloride parenterally in doses of 10,000 units three times daily for a period of about a month. This was followed by the oral use of vitamin B_1, 5 mg. daily, and by suitable orthopedic measures to prevent deformity as well as adequate physiotherapeutic measures.

Hecht Johansen [8] in 1931 first described a case of infectious mononucleosis complicated by encephalomeningitis. In 1931, Epstein and Dameshek [4] likewise reported a case of glandular fever with serous meningitis. Fledelius [5] in 1935 described a case of mononucleosis in the course of which a partial ocular motor paralysis took place, probably owing to an encephalitic process. He assumed that the encephalitis was brought about by the same agent which caused the infectious mononucleosis with its accompanying anginal symptoms. Sucher

and Schwarz [14] in 1936 reported a case of infectious mononucleosis complicated by encephalomeningitis, with mild right oculomotor paresis as well as left upper extremity paresis. Gsell,[6] in 1937, reported five cases of infectious mononucleosis, three of which were cases associated with acute serous meningitis and two with secondary facial paralysis which appeared as the main illness was on the decline. In 1938, Huber [7] reported a case of glandular fever complicated by hyperesthesia of the skin of both feet and a spinal fluid showing a pleocytosis of 333 cells, mostly lymphocytic elements, and a protein increase to 110 mg. per cent.

The etiology of infectious mononucleosis is not definitely known. The first impetus to a study of the problem was given by Murray, Webb and Swann [10] in 1926, who isolated *Bacterium monocytogenes,* apparently belonging to the group of Listerella, from rabbits having a generalized infection associated with an increase in the number of large mononuclear lymphocytes. Bland,[1, 2] in 1931, inoculated rabbits with the blood of patients at the height of the disease and then isolated a protozoan of the genus Toxoplasma from the rabbits, and believed that this was the cause of the disease. This could not be confirmed by other investigators.

Stimulated by these findings many workers began to look for a microbe in human patients. Nyfeldt,[11] in 1929, reported the isolation from the blood of an organism which he called *Bacterium monocytogenes hominis* and with which he produced the cellular blood picture in rabbits. Schmidt and Nyfeldt,[12] in 1938, reported five cases of infectious mononucleosis which were admitted to the hospital either with an angina or a peritonsillar abscess. One case, in addition, showed on admission clear signs of meningitis, whereas the other four, after having been afebrile for from two to 11 days, developed signs of meningitis and a spinal fluid indicative thereof, i.e., containing 6 to 138 cells per cu. mm. The blood culture in all five cases showed a growth of an organism of the Listerella group, one after four days, a second after six days, and three after 21 days. The spinal fluid also showed a similar growth; in the first case after six days, in the second case after nine days, and in the other three after 9, 11 and 21 days.

Soon doubt appeared as to the etiological significance of the Listerella group of organisms in the production of infectious mononucleosis, first because many observers had failed to confirm the isolation of the Listerella organism, and secondly because it had been recovered from the spinal fluid of cases afflicted with meningoencephalitis without any relation to infectious mononucleosis. Caspar Burn,[3] for example, grew Listerella from the blood of three newborn infants who had died in the New Haven Hospital from meningoencephalitis. Schultz, Terry, Brice and Gebhardt [13] isolated Listerella from spinal fluid of a nurse who was suddenly taken ill with fever, headache, stiffness of neck, doubtful Kernig sign, strabismus, ptosis of left eyelid, diplopia, facial twitch and lethargy. The spinal fluid was cloudy with 812 cells, 95 per cent of which were small lymphocytes. A rabbit inoculated intracerebrally with 0.5 c.c. of the spinal fluid developed a severe encephalitis two days after inoculation. The same organism was cultivated from the brain tissue of this animal.

McKinlay,[9] in 1935, in a study of 50 cases of infectious mononucleosis, found that repeated blood cultures were all negative and that emulsions of fresh glandular substance made during the acute stages and injected into monkeys and

guinea pigs were without demonstrable effect. It would thus seem that the Listerella group of organisms are secondary invaders or contaminations.

During the past year, some very interesting experiments which would point to a virus etiology have been performed. They have consisted for the most part of an attempt to transfer the disease to monkeys by means of lymph gland material from patients with infectious mononucleosis. Wising [17] summarizes his results as follows: "Fresh lymph gland obtained from two patients with infectious mononucleosis and injected into macacus monkeys, produced after 8 and 18 days, mild clinical symptoms with general lymphadenitis and a slight increase in the mononuclear cells of the blood. These changes could be reproduced in monkeys by injection of an emulsion from an extirpated lymph gland, in the one case in five passages, in the other case, in two. An assistant who, at the operation on monkey "Passage 3," pricked his finger with the knife which had just been used to divide the extirpated monkey lymph gland, felt ill the same day as monkey "Passage 4" with symptoms which appeared to be typical of infectious mononucleosis. All the author's attempts to isolate microörganisms from the blood of the patients taken during the initial febrile stage and from the affected lymph glands of both man and monkey, were unsuccessful.

Likewise, Van den Berghe and Liessens [15, 16] in 1939 inoculated a *Macacus rhesus* subcutaneously with the blood of a child having infectious mononucleosis and produced a syndrome which was characterized by lymphocytosis, leukopenia and a positive heterophile reaction. After filtering through a Seitz filter blood from patients with infectious mononucleosis, the authors succeeded in reproducing the disease in successive passages from monkey to monkey and this they did on many occasions. They concluded, therefore, that they were dealing with a filterable virus. They further attempted to culture the virus in tissue and were able, by means of a special medium consisting of a suspension of pieces of chicken embryos minced in Tyrode's fluid together with 10 per cent human serum, to preserve not only the virulence of the virus but to increase it by successive subculture.

It is common knowledge that some of the viruses have affinities for the central nervous system, and a number of diseases such as poliomyelitis, rabies and encephalitis are the result of the neurotropic properties of these viruses. On the other hand, many virus diseases such as measles and variola which usually do not show any affection of the central nervous system, in a few rare cases are complicated by encephalitis and myelitis. We may, therefore, assume that some viruses which usually have an affinity for organs other than the nervous system, in some cases may acquire neurotropic properties. It is further reasonable to conclude that in some cases of infectious mononucleosis the virus may also acquire neurotropic properties. In view of these facts, it seems to us that our case, which was characterized not only by a blood picture of infectious mononucleosis but also by a neurological picture of encephalomyelitis, was caused by one virus with neurotropic properties rather than by two different viruses.

Summary

1. A case of infectious mononucleosis with diffuse lower motor neurone disease in a man of 21 years, with recovery, is reported.

2. The literature of infectious mononucleosis complicated by involvement of the cerebrospinal nervous system is reviewed.

3. Recent experimental evidence supporting the theory that infectious mononucleosis is caused by a filterable virus is presented.

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UVEOPAROTITIS; CASE REPORT *

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Uveoparotitis (uveo-parotid fever or Heerfordt's syndrome) is a comparatively rare condition. Approximately 100 cases have been reported in the literature, the majority in Scandinavian and German journals of ophthalmology. No

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From the Department of Medicine, University of Wisconsin.

previous case has been so diagnosed at the Wisconsin General Hospital. The essential features are bilateral inflammatory lesions of the uveal tract and bilateral parotitis, often associated with paralyses of the cranial nerves, usually the peripheral portion of the seventh. The parotitis is of a chronic almost painless type, with a tendency to progress to resolution without suppuration. A low grade fever is generally present. The ocular manifestations commonly follow the glandular swelling, but may precede it or occur concomitantly. Usually the facial paralysis, when it occurs, follows the parotitis, but occasionally it, too, precedes or occurs simultaneously. In some cases the lacrimal, submaxillary and sublingual glands have also been involved. The majority of cases which have been reported have occurred in the second and third decades, but it may occur at any age. It is somewhat more prevalent in females and in the white race.

Uveoparotitis, as a clinical syndrome, was first recognized in 1909 by the ophthalmologist Heerfordt of Copenhagen.[1] He expressed the belief that the disease was an atypical form of mumps. Since that time many different etiologic factors have been proposed. The majority of clinicians and pathologists seem now to be of the opinion that tuberculosis is the primary factor. The case for a tuberculous etiology was well presented by Garland and Thomson in 1933.[2] They even termed the condition "uveo-parotid tuberculosis." They state that in no case in which a biopsy was performed was histologic evidence of tuberculosis lacking. Some observers, on the other hand, are opposed to the theory of tuberculosis as the cause of the condition. This opposition is based on the results of animal inoculations and tuberculin tests which are more often negative than positive, and on the clinical observation that these patients seldom show the more common symptoms or signs of tuberculosis. It does not lie within the scope of this report to enter into any detailed discussion of this controversial point, but inasmuch as Dr. Max Pinner very kindly reviewed the biopsy from the parotid gland in this case and has written several articles on noncaseating tuberculosis within the past few years, a brief résumé of his conclusions on the subject will be presented.[3] He states that from a study of the literature it seems quite likely that so-called uveo-parotid fever belongs in the general classification of noncaseating tuberculosis. Boeck's sarcoid, osteitis tuberculosea multiplex cystoides, certain cases of Mikulicz's syndrome, and a number of disseminated pulmonary and lymph node lesions would also be included. He points out that clinically, noncaseating tuberculosis is a rather benign chronic disease, showing a certain tendency to intermittence and recurrence. Histologically, as far as material is available, there "is not only uniformity but monotony" in regard to the lesions. Biologically it is of interest to note that a large percentage of these patients with noncaseating tuberculosis, as far as they were tested, reacted only slightly or not at all to tuberculin. (However, Pinner feels that this is apparently not the anergy of the non-infected organism, since in a respectable number of patients it was possible to show that they have tuberculin neutralizing substances, anticutines, in their serum.) He summarizes the circumstantial and indirect evidence for the etiological nature of this group of diseases as follows: (1) The histological characteristics of the lesions. (2) The demonstration of anticutines and therewith of positive tuberculin anergy. (3) The fact that practically all patients who expired died of frank tuberculosis.

Our patient, a 36-year-old married white female, was first admitted to the Medical Service of the Wisconsin General Hospital on September 20, 1938. Her chief complaint was swelling of the parotid glands bilaterally. She had felt perfectly well until about three months previously, at which time she had contracted a severe "cold." She had driven with the car window open, exposing the left side of her face to a draft. The muscles of the left face suddenly became paralyzed. She next noticed sore eyes. A diagnosis of iritis was made at a local clinic and she was treated with typhoid vaccine. The facial paralysis gradually improved. About five weeks before

FIG. 1.

admission tonsillectomy was performed. Within 48 hours the patient noted tender swellings in front of the ears, associated with marked dryness of the mouth. The height of the swelling occurred about four weeks before admission, since which time there had been a gradual decrease of the bilateral parotid enlargement and a progressive increase in the amount of saliva present.

Inventory by systems added only photophobia and a 25-pound weight loss in the past three months. Past history established the occurrence of bilateral mumps four years ago. Social and family histories were non-contributory. There was no known tuberculosis in the family.

Physical examination showed a well nourished woman of the pyknic type. There was evident enlargement of the parotid glands bilaterally, the left being considerably larger than the right (figure 1). The enlarged parotid glands were firm and nontender. The submaxillary glands were moderately enlarged, but were not of so firm a consistency as the parotids. The upper eyelids showed slight edema, but there was no enlargement of the lacrimal glands; the extraocular movements were normal; there was slight circumcorneal injection of each eyeball. The pupils were dilated and fixed (atropine had been used daily previous to admission). The irides lacked their normal clearness. The fundi were not abnormal. An ophthalmologist reported the presence

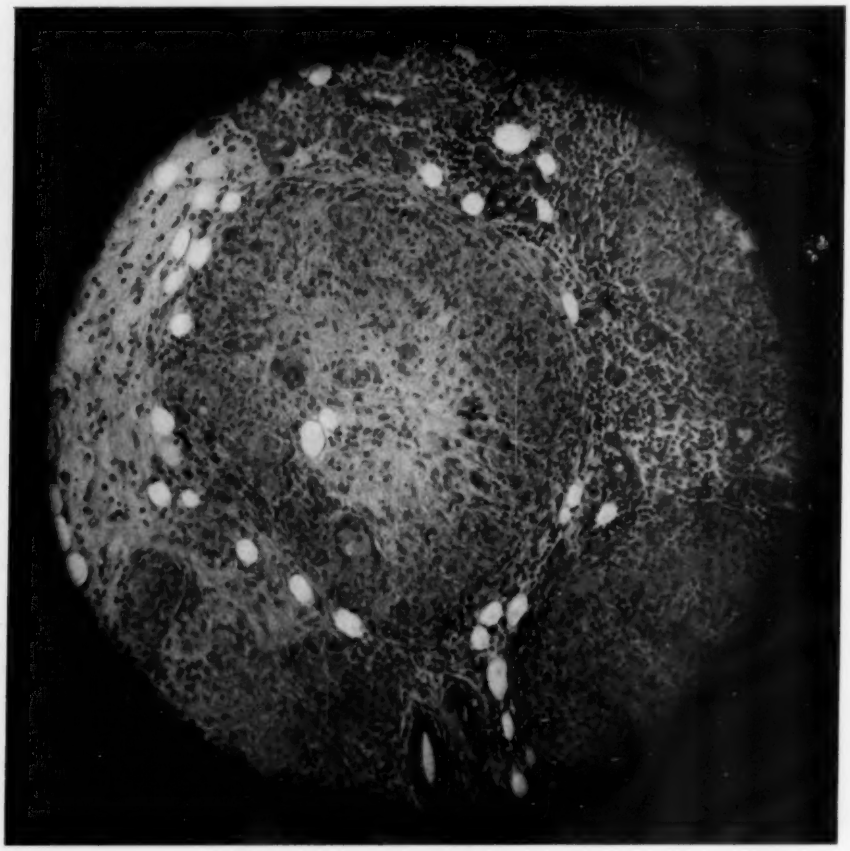

FIG. 2.

of keratitis punctata on the left, believed to be in Descemet's membrane. There was slight facial asymmetry, with a decreased nasolabial fold on the left, but no residual facial paralysis. A thyroidectomy scar was present. Blood pressure was 100 mm. Hg systolic and 76 mm. diastolic. The tip of the spleen was just palpable on deep inspiration. The highest temperature recorded during her 25-day hospitalization was 99.8° F. The usual range was 98° to 99.2° F.

Laboratory studies showed hemoglobin 15 grams, red blood cells 4,700,000, white blood cells 5,038, with 71.6 per cent neutrophiles, 2.6 per cent eosinophiles, 0.4 per cent basophiles, 14.2 per cent small lymphocytes, 3 per cent large lymphocytes, 7 per

cent monocytes, 0.6 per cent large young cells, and 0.6 per cent unclassified cells. The blood Wassermann reaction was negative. Spinal fluid showed protein 54 mg. per cent, sugar 53 mg. per cent, gold sol 1221100000, Ross Jones and Noguchi reactions faintly positive and one cell per cu. mm. Chest roentgen-ray showed no evidence of recent or active parenchymal infiltration. There was no evidence of any osseous disease in the skull, spine or right femur. Biopsy of the left parotid gland showed the gland largely replaced by epithelioid hyperplasia and tubercle formation. A few atypical giant cells were seen. There was considerable lymphocytic infiltration (figure 2). A section was sent to Dr. Max Pinner, who concurred in the diagnosis of

FIG. 3.

noncaseating tuberculosis. A Mantoux test with 0.01 mg. old tuberculin was negative, but positive with 1.0 mg.

On the advice of consultants from the Chest and Radiologic Services, the patient received three radiations of 150 r. each over the left parotid on alternate days. There was no immediate adverse or favorable reaction. She also received vitamins A, C and D in excess of those contained in an adequate diet. The uveitis was treated with 1 per cent atropine b.i.d., warm compresses t.i.d., and 5 per cent dionin at night.

At the request of the radiologic consultant she returned in December 1938. At this time there was no evidence of the previous parotid swelling (figure 3). The submaxillary lymph glands had decreased in size but remained just palpable. An

ophthalmologist considered her eyes "greatly improved" but advised further observation. There were no symptoms referable to the eyes at this time. The tip of the spleen remained palpable. The blood count and sedimentation rate were within normal limits. A roentgenogram of the chest showed no change. There was no temperature elevation above 99° F. during her eight-day hospitalization. She was again given three radiations of the same dosage as previously, over the left parotid gland.

During the following 14 months the patient was examined at intervals in the Outpatient Department. All symptoms and signs progressively diminished to complete disappearance. Further irradiation of the parotid and treatment of the eyes were not deemed necessary. She was last admitted to the hospital in February 1940. She returned at this time at our request for complete progress studies. She stated that she felt perfectly well. She had gained 18 pounds in weight. The eyes were considered entirely normal on this occasion. No residuals of the previous extensive changes were determined. It is of interest that at this time she had a positive Mantoux test with 0.01 mg. of old tuberculin.

The prognosis in this disease is generally conceded to be good as to life and fair as to residua. Only four deaths have been reported in the literature, and of these, three were due to miliary tuberculosis.[4] There is usually no permanent impairment of the general health, and the parotitis and nerve paralyses almost invariably disappear. There may be permanent impairment of visual acuity, however, and recurrences of the uveitis, even ultimately resulting in blindness, are not uncommon.

Inasmuch, then, as this condition usually undergoes spontaneous resolution, one must obviously be very guarded in giving any particular form of treatment too much credit for a "cure."

Summary

A case of uveoparotitis, a comparatively rare affection, is presented. The etiology, course, treatment and prognosis are briefly discussed.

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CHRONIC MENINGOCOCCEMIA COMPLICATED BY ACUTE ENDOCARDITIS*

By Robert B. Nye, M.D., F.A.C.P., Charles W. Semisch, III, M.D., and Louis Merves, M.D., *Philadelphia, Pennsylvania*

The etiological agent of epidemic cerebrospinal meningitis, the meningococcus, was first described in 1887 by Weichselbaum. Gwyn [1] demonstrated the meningococcus in the blood stream. W. W. Herrick, who has had a very extensive experience with meningococcic infections, divided the infection into three stages, viz: (1) local invasion of the upper respiratory tract, (2) invasion of the blood stream, (3) metastatic localization. It is the consensus of opinion at present [2] that in the pathogenesis of epidemic cerebrospinal meningitis, the pathway of infection is via blood stream rather than by direct extension from the nasopharynx, and that the process may terminate at any stage, the latter fact being attested to by the increasing number of meningococcemias reported in recent years without any localizing manifestations.

In our review of the American literature we have chosen 69 cases of chronic meningococcus septicemia and have excluded those cases of the so-called "Waterhouse-Friderichsen syndrome" (acute fulminating meningococcic septicemia with bilateral adrenal hemorrhages).

Chronic meningococcemia without meningitis was first reported in Germany by Solomon in 1902.[3] Since then there have appeared sporadically in the literature presentations of similar cases. Carbonell and Campbell [4] critically reviewed the literature to 1938 and accepted 30 cases to which they added three of their own. The three cases which they observed were treated with anti-meningococcic serum and all recovered. The septicemia was complicated by meningitis in 42.4 per cent of the cases, endocarditis in 12.1 per cent, with a total mortality rate of 9.1 per cent.

At about this time Appelbaum [5] collected 15 cases in the Bellevue Hospital in New York. Of these, 46 per cent developed meningitis, 20 per cent endocarditis; the total mortality rate for this series was 13.3 per cent. He noted that blood culture rarely was positive until the third week of the disease, and stated that the patient's serum does not as a rule agglutinate meningococci.

Since then there have appeared further reports. Krusen and Elkins [6] presented a case of chronic meningococcemia and associated endocarditis which was treated with fever therapy and intravenous prontosil with recovery. Willius and Eaton [7] observed a case of chronic meningococcemia complicated by endocarditis with death despite intensive serum therapy. Heinle [8] presented five cases with three deaths. Of these, two were complicated by endocarditis, and the third, after a 14 year history of recurrences, finally succumbed to cerebral hemorrhage. The two patients who recovered were treated with antiserum and with meningococcus vaccine respectively. Binns and Clancy [9] reported two cases cured by sulfanilamide. Goundry and Phalen [10] successfully treated one case with serum. Rosenbluth and Stetten [11] reported a case of meningococcic septicemia complicated by meningitis. The meningitis subsided with serum

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From the Department of Therapeutics, Jefferson Medical College Hospital.

therapy, but the septicemia persisted. Fever therapy was administered with complete recovery. Zendel and Greenberg [12] reported two cases, the first of which was treated with antitoxin, antiserum and sulfanilamide. The second was treated with sulfanilamide alone. Both cases recovered. Top and Young [13] treated one case with antitoxin (Ferry) which was found to be ineffective. Antiserum was then given with complete success. Schwentker, Gelman and Long [14] treated one case with sulfanilamide with recovery. Hennell and Weiner [15] observed a case of chronic meningococcemia complicated with endocarditis which resulted in death. Long and Bliss [16] reported five cases treated with sulfanilamide with recovery.

TABLE I

Author	No. cases observed	No. deaths	Autopsy
Gwyn	1	1	Yes
McMahon and Burkhart	1	1	Yes
Rhodes	1	1	Yes
Warfield and Walker	1	1	Yes
Cecil and Soper	1	1	Yes
Finley and Rhea	1	1	Yes
Hennell and Weiner	1	1	No
Krusen and Elkins	1	0	Recovery
Willius and Eaton	1	1	Yes
Heinle	2	2	No
Masters	3	0	Recovery
Hyland	1	1	Yes
Appelbaum	3	0	Recovery
	18	11	
Authors' case	1	1	Yes
	19	12	

Incidence of endocarditis 27.1 per cent.
Mortality rate when complicated by acute endocarditis 63.2 per cent.

In table 1 are listed the cases of endocarditis complicating meningococcic septicemia. In the seven cases of endocarditis which recovered the etiology is doubtful, as there was a history of rheumatic infection and abnormal heart sounds in several instances. Further than this, it is a fact that fever and anemia may produce cardiac murmurs without any demonstrable structural change. The case report presented is noteworthy in that there is no previous history of heart damage. At the onset of the present illness the heart appeared to be normal by physical examination and by electrocardiograms.

CASE REPORT

G. W., male, white, aged 20, had been discharged from this hospital two years previously with a diagnosis of diabetes mellitus and balanoposthitis. One month prior to admission, following a seashore excursion, he awakened with a severe head cold and pain in the right ear. After two days his family doctor was consulted; he found the patient suffering with a discharge from the right ear, cough with expectoration, and slight fever. His ear was treated intermittently for two weeks and the discharge ceased. A week prior to admission he awakened with chills, vomited, and within a few hours had a high fever and profuse sweats. The following day he com-

plained of marked malaise and first noted the appearance of "red spots" over the entire body. The family doctor was again consulted, a diagnosis of acute rheumatic fever was made, and treatment was carried out on that basis. Chills and fever continued, joint pains developed, the red spots persisted, and hospitalization was advised. He was admitted to the medical service on September 7, 1939, complaining of chills and fever, arthralgia and myalgia, and a generalized eruption of a week's duration.

On physical examination the patient was a young athletic male who appeared acutely ill. The ears grossly were normal. There was photophobia. The pharynx was injected, the tonsils enlarged and inflamed. Examination of the lungs was negative. The heart was normal in size and position; no abnormalities of rhythm or heart sounds were detected. Abdominal examination was negative. There was no swelling or redness of the joints, but they were tender and painful on motion, the pain being more marked in the third toes of both feet. There were numerous small subcutaneous swellings throughout both extremities that were painful and not well circumscribed. There was a generalized maculopapular, pustular, violaceous eruption, which did not blanch on pressure; the only parts of the body free from these lesions were the palms of the hands and the hairy regions. The temperature was 100⅘° F., pulse rate 94, respiratory rate 22, blood pressure 116 mm. Hg systolic and 64 mm. diastolic, hemoglobin 84 per cent, red blood cells 4,200,000, white blood cells 9,600, color index 1.0, neutrophiles 80 per cent, lymphocytes 18 per cent, myelocytes 2 per cent. Urine examination was negative; blood sugar was 51 milligrams per 100 c.c. The diagnostic possibilities considered at this time were: one of the infectious fevers, acute rheumatic fever, bacterial endocarditis, tuberculosis, malaria, and chronic meningococcemia.

Laboratory Findings: Wassermann and Kahn tests were negative. Weil-Felix reaction was negative. Agglutination and skin tests for undulant fever were negative. Gonococcic complement fixation test was negative. No plasmodia were found in the blood smears. Stool studies were negative for typhoid bacilli. Seven consecutive blood cultures were negative until October 12 (five weeks after admission), at which time the meningococcus was recovered, there being less than five colonies per cubic centimeter. Spinal fluid examinations were negative on three occasions. Blood coagulation studies and platelet count were normal. The roentgenologic study of the chest on September 18 was reported as probable acute tracheobronchitis with the possibility of Hodgkin's disease. On September 20 roentgen-ray of the ear regions showed chronic mastoiditis on the right side with possible activity.

Course: Since an etiological diagnosis was not possible at first, treatment was symptomatic. On September 28 an accentuated first sound was heard at the mitral area. The spleen was questionably palpable. It was noted that as the rash disappeared the temperature dropped several degrees. The otologist reported contraction and thickening of the right tympanic membrane. On October 9 a diastolic murmur at the mitral area was noted, and later a systolic murmur developed. The patient complained of occasional bouts of pain in the left hypochondrium. At no time were red blood cells, albumin, or casts noted in the urine. At this time bacterial endocarditis was the tentative diagnosis. A course of sulfapyridine therapy was begun on October 6, the first positive blood culture being obtained on October 12, six days later. A specimen of the culture was sent to Dr. Sara Branham at the U. S. Public Health Service for typing. Sulfapyridine was continued, and because a satisfactory blood level was not being secured, on October 22, 10 grams of sodium sulfapyridine were given intravenously in a liter of physiological salt solution. A maximum blood concentration of 9.1 milligrams per 100 cubic centimeters of blood was secured at this time. The agglutination titer of the patient's serum against the organisms isolated by blood culture and against a known strain of meningococcus was 1:160 on October 18.

On October 28 the patient's condition became critical. For the first time his diabetes presented a serious problem. The patient was uncoöperative and refused nourishment. Blood culture on October 30 was positive for meningococcus, with 200 colonies per cubic centimeter. The hemoglobin and red blood cells had dropped. On October 29 the agglutination titer had dropped to 1:40, and serum therapy was started with polyvalent antimeningococcic serum. The following day the patient developed

FIG. 1. Arrow indicates vegetation on mitral valve.

signs of fluid in the right hemithorax. Thoracentesis was done and 4 c.c. of cloudy fluid obtained which yielded no growth. Roentgen-ray examination of the chest at this time revealed an extensive atypical pneumonia, and a probable bilateral pleural collection of fluid.

On November 1 the patient was in a semistuporous state. Blood sugar was 400 milligrams, carbon dioxide combining power was 36, non-protein nitrogen 68. The

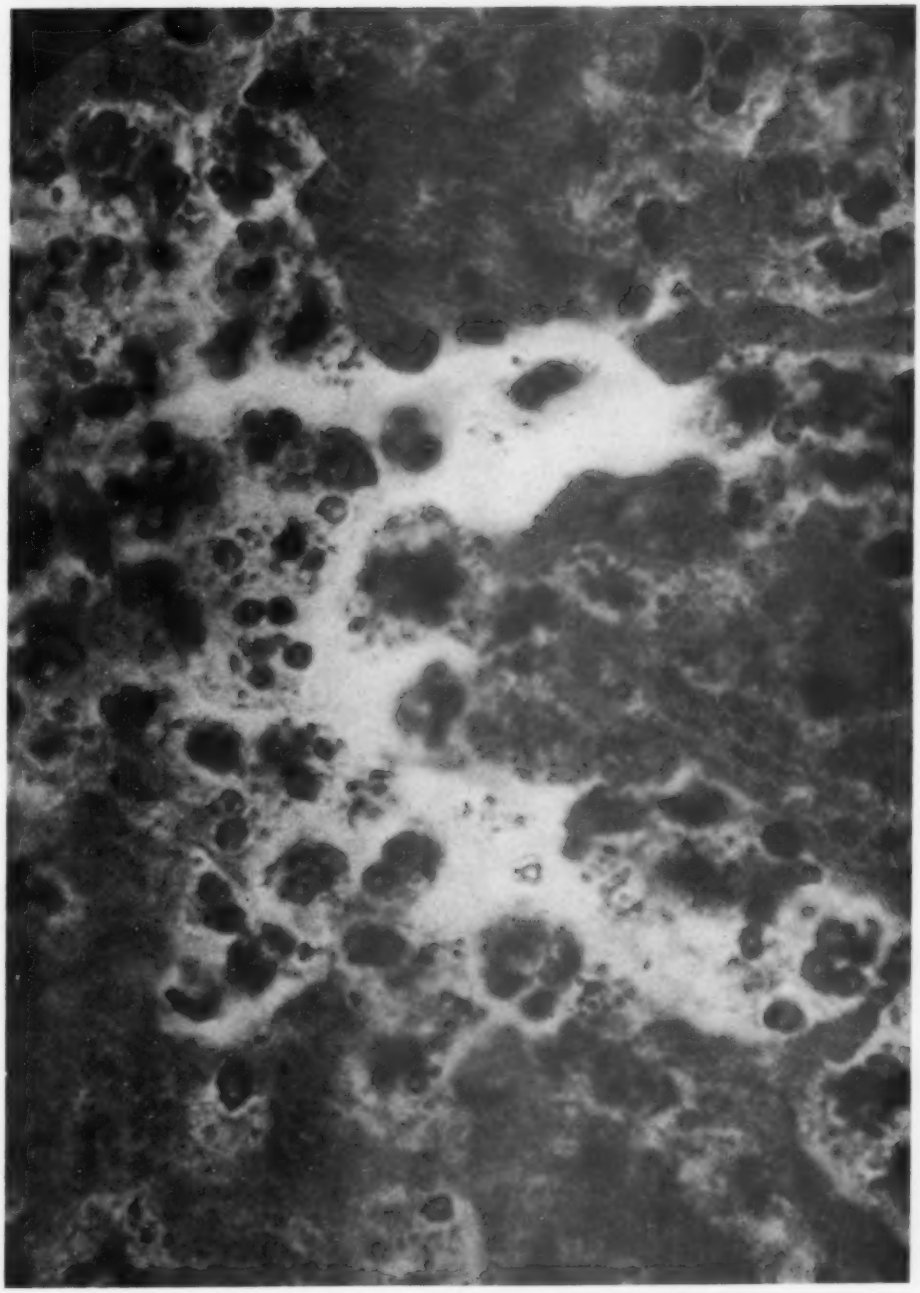

FIG. 2. Microphotograph of section through the mitral valve showing intracellular diplococci (× 1200).

only significant electrocardiographic finding was reported on November 1, at which time there was a tachycardia and a diphasic T-wave in LIVCF–3. Transfusions were given on November 1, 2, and 3, of 500 c.c. of citrated whole blood. On November 2 the U. S. Public Health Service reported Meningococcus Type II. A new lot of serum which was particularly high in type II antibodies was secured and its intravenous administration begun. At this time the agglutination titer determination was incomplete agglutination at 1:40. The patient seemed better, although his temperature and pulse showed no significant change. On November 5, 1939, the patient suddenly died.

Autopsy Findings: There were small pericardial and peritoneal effusions. The heart weighed 360 grams. The epicardial surface was smooth, moist and glistening. On the atrial surface of the anterior mitral leaflet there was a large vegetation which measured approximately three centimeters at its base. It was firmly adherent and around its edges the endocardial lining revealed definite ulceration (figure 1). The remaining valve cusps were normal. An acute ulcerative and vegetative endocarditis

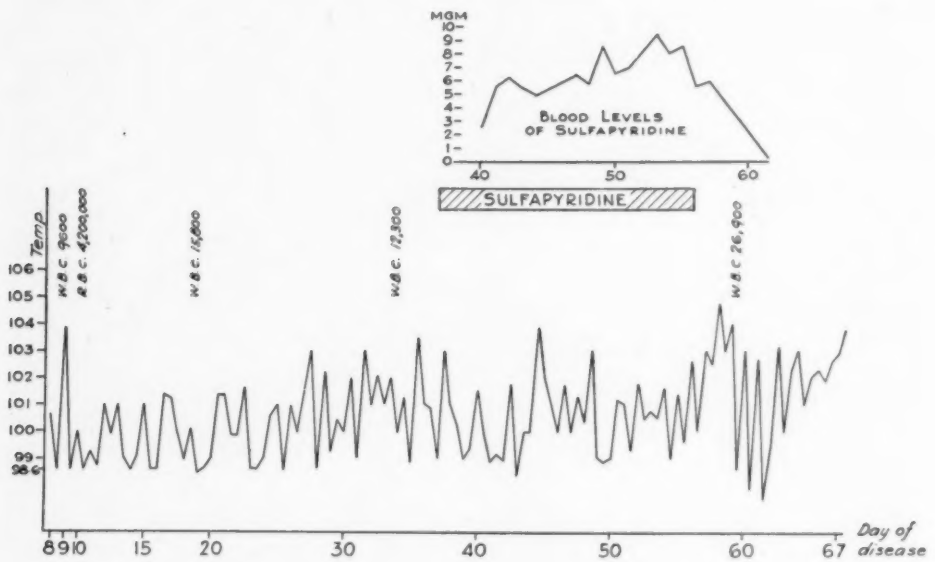

FIG. 3. Graph showing temperature curve, representative leukocyte counts, and sulfapyridine levels.

of the mitral valve was present. In sections made through the mitral valve, bean-shaped diplococci were seen within the cytoplasm of the polymorphonuclear leukocytes (figure 2). Multiple infarcts of the spleen and kidney were demonstrable. There was partial atelectasis of the right lung. There was no evidence of meningitis. The only abnormal finding in the brain was a small area of softening in the rostral portion at the base of the pons.

DISCUSSION

Chronic meningococcemia is a disease entity characterized by (1) intermittent chills, fever and sweats, (2) maculopapular rash occurring in crops, (3) myalgia and arthralgia, (4) moderate polymorphonuclear leukocytosis, (5) positive blood cultures, usually not obtained before the third week, and (6) variable

duration of one to 30 weeks, though in one of the cases reviewed (Heinle, supra vide) there is a history of recurrences extending over 14 years.

Herrick [17] states that the two most serious and most frequently occurring complications of meningococcic sepsis are meningitis and endocarditis, and that in the latter the lesions are usually present on the mitral and aortic valves. The disease runs an acute or subacute course and almost always ends fatally. This is fully borne out by the autopsy findings in the cases noted.

In the present case sulfapyridine administration was begun six days before the first positive blood culture was obtained. When the literature was reviewed it was learned that Dimson [18] and Hobson and McQuaide [19] had treated meningococcic infection successfully with M & B 693, and on this basis sulfapyridine was continued. Despite adequate therapeutic dosage, no beneficial effect was observed, and the disease progressed. When the agglutination titer of the patient's serum dropped, antiserum was given intravenously, with little hope and no expectation of preventing a fatality in the face of the already established bacterial endocarditis.

We believe that in this case sulfapyridine was given a fair trial, and that it did not influence the course of the disease. It obviously did not prevent the localization in the mitral valve area.

Polyvalent antiserum was given late in the illness. It is an accepted fact that it reduces the mortality rate in epidemics of meningococcic meningitis from 70 per cent to between 11 per cent and 30 per cent (Topley and Wilson [2]). In view of the proved efficiency of the antiserum we believe it should be used in meningococcic infection as soon as an etiological diagnosis has been made.

Insofar as the use of sulfanilamide in conjunction with serum therapy is concerned, the work of Branham and Rosenthal [20] on experimental animals would indicate a synergistic action, the combined effect being greater than either component alone. Waghelstein [21] studied a series of 106 patients suffering from meningococcic infections to determine the value of sulfanilamide. Seventy-two were treated with sulfanilamide, yielding a mortality rate of 12 per cent, whereas the mortality in the 34 cases treated with serum and sulfanilamide was 13 per cent. These results compare favorably with the experience of those who used serum alone in epidemics of meningitis. It would seem, theoretically at least, that the use of bacteriostatic agent (sulfanilamide) combined with a specific antibacterial serum is highly desirable.

Conclusions

1. The American literature is reviewed and a case reported of chronic meningococcemia complicated by endocarditis, proved by bacteriologic and postmortem findings.

2. The mortality of meningococcic sepsis complicated by endocarditis in the cases to date is 63 per cent.

3. It would seem that the rational procedure in the treatment of this disease would be the use of sulfanilamide and antiserum, type specific where possible.

4. The disease entity is sufficiently characteristic clinically to warrant bedside diagnosis.

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EDITORIAL

SOME INDICATIONS AND CONTRAINDICATIONS FOR SPLENECTOMY

THE spleen has long been known to include among its functions an important rôle in the production of the formed elements of the blood and also in their eventual elimination from the circulation. These functions are dependent primarily upon the reticuloendothelial cells in the spleen, and they are shared in varying degree by other organs and tissues which contain such cells. In the normal adult the part which the spleen plays directly in contributing new cells to the circulation is insignificant and is limited probably to the production of a few lymphocytes and monocytes. In certain types of anemia, however, particularly those in which bone marrow is displaced or destroyed, compensatory active extramedullary hematopoiesis often occurs. This may involve any of the types of blood cells, and in it the spleen usually plays a prominent part.

Under normal conditions the spleen in common with other reticuloendothelial tissues is actively concerned with the removal of cells from the circulation, largely by phagocytosis. The part it plays in the removal of red blood cells is well established. It is generally believed that platelets are similarly removed. It is also likely that various types of leukocytes are taken up and destroyed in the spleen, although the number so disposed of is probably insignificant compared with those which migrate into or are excreted into the lumen of the gastrointestinal and respiratory tracts. Normally this process is presumably limited to the removal of aging or defective cells. At least the rate of removal and the rate of cell production are so nicely adjusted that only slight fluctuations occur in the number of circulating cells.

Under pathological conditions, however, the rate of cell destruction may be so accelerated that a serious cell deficiency develops. This is well established in the case of the red cells in familial hemolytic jaundice, and in the case of the platelets in essential thrombocytopenic purpura. There is still a question as to whether this depends primarily upon a defect in the cells resulting from faulty production, or upon a pernicious overactivity of the spleen. That the degree of activity is excessive from the standpoint of the wellfare of the patient is shown by the excellent clinical results which follow splenectomy, quite regularly in familial hemolytic jaundice and frequently in essential thrombocytopenic purpura.

Hitherto little attention has been paid to the possibility of an analogous disturbance in which the leukocytes are primarily destroyed. In 1938, however, Wiseman and Doan[1] in a preliminary report described three cases

[1] WISEMAN, B. K., and DOAN, C. A.: A newly recognized granulocytopenic syndrome caused by excessive splenic leukolysis and successfully treated by splenectomy, Jr. Clin. Invest., 1939, xviii, 473.

which apparently fit into such a category, and in this number of the ANNALS OF INTERNAL MEDICINE they are reporting five such cases in detail under the designation "primary splenic neutropenia." These cases complained chiefly of weakness, fever, and coryza or angina. They showed a marked leukopenia and granulocytopenia together with a progressive enlargement of the spleen. Leukemia and ordinary malignant neutropenia were excluded by examining aspirates of sternal marrow, which showed active hyperplasia involving chiefly the neutrophilic myelocytes. The spleens in all cases were removed and showed an extraordinary ingestion of neutrophilic leukocytes by the splenic phagocytes. In some cases the presence of anemia and of thrombocytopenia and bleeding indicated that this hyperactivity of the spleen is not necessarily restricted to the leukocytes, but may extend also to the red cells and platelets.

The view of Wiseman and Doan that the spleen is primarily at fault receives support from the great rapidity with which the leukocyte count rose after operation, often reaching normal a few hours after the splenic pedicle was ligated. It is also supported by the sustained clinical improvement observed in all these cases after splenectomy. Furthermore one patient subsequently survived a severe attack of erysipelas and showed a normal leukocytic response to the infection. The importance of recognizing such cases early and giving them the benefit of splenectomy is obvious, in view of the futility of other methods of treatment. As these authors point out, however, a precise diagnosis is essential before resorting to such a radical procedure.

The successful results usually obtained by splenectomy in these diseases as well as in occasional cases of acquired hemolytic jaundice and Banti's syndrome have led in some clinics to the indiscriminate use of the operation in cases of refractory anemia of obscure origin. In some cases, as in unrecognized leukopenic leukemia, the operation is dangerous and futile, and in some it is positively harmful. Aside from the immediate risk from the operation, the greatest direct injury is inflicted on those cases whose splenic enlargement is owing to a compensatory extramedullary hematopoiesis. Radiation, if effective, is similarly harmful. Splenic hyperplasia of this type may occur in some severe hemolytic anemias, such as Cooley's Mediterranean anemia, in which the bone marrow, although hyperplastic, is unable to keep pace with the rate of cell destruction. It is seen most commonly, however, in the myelophthisic anemias, in which the marrow cells are injured or crowded out by various foreign tissues. In addition to the well known conditions which give rise to anemias of this type, there is a group of obscure origin which run a chronic course and are often mistaken for chronic myeloid leukemia because of the changes in the blood. There is a severe anemia and a marked leukocytosis with many myelocytes and normoblasts, and often cells even more primitive in type. Some cases, however, have been mistaken for Hodgkin's disease, Banti's disease, and even neoplasms of the spleen.

Cases of this type have been reported under many different terms; for example by Hickling [2] as "chronic non-leukemic myelosis," and by Vaughn and Harrison [3] as myelosclerosis. Ten such cases have been described by Jackson et al.[4] and more recently five others by Reich and Rumsey [5] as "agnogenic myeloid metaplasia of the spleen." As Jackson has pointed out, an accurate diagnosis requires not only a thorough physical examination and a study of the blood but also an adequate examination of the sternal marrow and the spleen.

The marrow in these cases has not shown any constant characteristic changes, but it is not leukemic. In some cases the cells have been replaced in varying degree by fibrous tissue and even by new bone. Roentgenograms of the bones, however, are often normal, even in the presence of fibrosis, and in some cases the marrow has been described as normal or hyperplastic. The distinctive feature is the occurrence of areas of hematopoiesis in the spleen. In some cases material obtained by puncture may suffice for diagnosis, but in others an actual biopsy of both organs may be required. The necessity for an accurate diagnosis is indicated by the fact that many of these 15 cases were subjected to splenectomy or radiation, and all were injured by these measures. The anemia was aggravated, transfusions were required more frequently, and in some death was manifestly hastened.

Splenectomy is invaluable in saving life and restoring health in properly selected cases in which the diagnosis is established. On the other hand it is a very dangerous procedure to use blindly as a measure of last resort. It should not be employed unless there is a positive indication for its use, and it should be deferred until all possible means have been taken to exclude diseases in which it is useless or harmful. Examination of the marrow is often required to accomplish this, and sometimes also of the spleen.

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REVIEWS

Nutritional Deficiencies; Diagnosis and Treatment. By JOHN B. YOUMANS, A.B., M.S., M.D., assisted by E. WHITE PATTON, M.D. 385 pages; 23.5 × 16 cm. J. B. Lippincott Co., Philadelphia. 1941. Price, $5.00.

This volume is offered not as a treatise on deficiency diseases for the dietitian or investigator, but as a reliable source of information for the busy physician, bringing to him in an orderly manner the essential basic facts gleaned from an exhaustive study of the existing literature concerning the clinical manifestations of these disorders.

Only those facts directly applicable to man are included, and such work as may be still called controversial has been omitted. Particular attention is devoted to the recognition and treatment of the principal avitaminoses. Iron and iodine deficiency is also thoroughly discussed, the more uncommon mineral deficiencies being briefly covered.

Each chapter is well organized and clearly written. Footnotes have been omitted. References are few but well chosen. An appendix containing methods of laboratory diagnosis, and a tabular summary of the vitamins with principal dietary sources are given. Illustrations are few but appropriate.

To the internist or general practitioner this book can be recommended as a means of arriving at an intelligent solution of the problem of the treatment of the avitaminoses without recourse to the voluminous literature on these subjects.

J. W.

Diseases of Metabolism. Edited by GARFIELD G. DUNCAN, M.D. 985 pages; 17 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1942.

In his preface to this work the Editor discusses the problems of presentation of a book on metabolism and outlines his aim as an attempt "to provide for the physician a practical basis for the understanding, diagnosis and treatment of the various metabolic disorders." There can be no doubt that he has been most successful in presenting a well organized, interesting and complete volume.

The first five chapters discuss metabolism of carbohydrate, protein, lipids and minerals, and are written by G. G. Duncan, C. N. H. Long, Abraham White, and Abraham Cantarow. Water balance is next treated by J. P. Peters, nutritional and metabolic aspects of diseases of the blood by L. M. Tocantins, and vitamins and avitaminosis by T. D. Spies and H. R. Butt. Chapters on undernutrition and obesity are written by L. H. Newburgh and Frank A. Evans, xanthomatoses by E. Mason, gout by Bauer and Klemperer, and diabetes insipidus and diseases of carbohydrate metabolism by G. G. Duncan and A. Cantarow.

It is impossible, in a short review, to do justice to a work of such character and merit. The reviewer believes that it can be fully recommended.

T. N. C.

Immunology. By NOBLE PIERCE SHERWOOD, Ph.D., M.D., F.A.C.P., Professor of Bacteriology, University of Kansas, and Pathologist to The Lawrence Memorial Hospital, Lawrence, Kansas. Second edition. 639 pages; 15.5 × 23.5 cm. C. V. Mosby Co., St. Louis. 1941. Price, $6.50.

Published first in 1935, the second edition of this textbook gives evidence of careful revision. Much old material has been removed and the results of recent investigations have been incorporated. This has occasionally required the rewriting of whole sections. New chapters have been added on the reticulo-endothelial system and serum sickness. Many transpositions of material have been made, both within and among

chapters. This has led to greater continuity of thought and clarity of presentation. The illustrations on the whole are helpful and the references appended to each chapter are adequate. The total impression gained is that the book has been greatly improved and should be of value to medical and other students interested in immunology and serology.

F. W. H.

Handbook of Communicable Diseases. By FRANKLIN H. TOP, A.B., M.D., M.P.H., and collaborators. 682 pages; 23.5 × 15.5 cm. C. V. Mosby Co., St. Louis. 1941. Price, $7.50.

This is an interesting book which one thoroughly enjoys. Reading this handbook is a pleasure for many reasons, among which are its large print, its unity and coherence, and its concise information.

The whole book is extremely well organized. Diseases are classified according to the common portal of entry, and the descriptions of the individual diseases follow a uniform plan. Specific nursing care is stressed for each of the different infections. The illustrations are splendid.

Dr. Top's book seems to be more than just a handbook, since it contains such a wealth of material without being too detailed, and yet it is written in a flowing, interesting style.

W. M. S.

COLLEGE NEWS NOTES

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged.

Books

Dr. Lewellys F. Barker, F.A.C.P., Baltimore, Md.—"Time and the Physician";
Dr. Edward L. Hanes, F.A.C.P., Webster, N. Y.—"The Minds and Nerves of Soldiers";
Dr. Edward B. Krumbhaar, F.A.C.P., Philadelphia, Pa.—"A History of Medicine" (a translation from Arturo Castiglioni);
Dr. Herbert Pollack, F.A.C.P., New York, N. Y.—"Modern Diabetic Care";
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—"Elimination Diets and Patient's Allergies."
Dr. Abraham Rudy, F.A.C.P., Boston, Mass.—"Simplified Diabetic Manual";
Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—"Vitamin Therapy in General Practice."

Reprints

Walter M. Bartlett, F.A.C.P., Captain, (MRC), U. S. Army—1 reprint;
J. Edward Berk (Associate), Lieutenant, (MRC), U. S. Army—1 reprint;
Dr. John A. Foley, F.A.C.P., Boston, Mass.—1 reprint;
Dr. John Harvey, F.A.C.P., Lexington, Ky.—1 reprint;
Dr. John Harlan Hornbaker, F.A.C.P., Hagerstown, Md.—2 reprints;
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Estelle E. Kleiber, F.A.C.P., New Brunswick, N. J.—2 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—2 reprints;
Frank B. Queen, F.A.C.P., Major, (MRC), U. S. Army—1 reprint;
Dr. John W. Scott, F.A.C.P., Lexington, Ky.—3 reprints;
Dr. Thornton Scott (Associate), Lexington, Ky.—4 reprints;
Dr. Walter Wessels, F.A.C.P., Los Angeles, Calif.—2 reprints;
Dr. Willard R. Wirth, F.A.C.P., New Orleans, La.—1 reprint.

Dr. Samuel Johnston, F.A.C.P., Toronto, Ont., was elected President of the Academy of Medicine of Toronto at its 35th Annual Meeting on May 5, 1942. The Academy's Fellowship numbers 1198, of whom about 16 per cent are on active military service. The Academy is helping to provide medical libraries for overseas medical units recruited from the Toronto district. Its local library now contains more than thirty thousand volumes.

Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif., was elected President of the Society of Neurology and Psychiatry of Northern California at its last meeting, April 19, 1942.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., presented a paper on "Nutrition as It Applies to General Disease," illustrated by a motion picture in natural color, at a meeting of the Lehigh County Medical Society in Allentown, Pa., May 12, 1942.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., presented a paper on "Liver Therapy and Vitamin-B Complex in Cirrhosis of the Liver and Atrophic Gastritis" at the 176th Annual Meeting of the State Medical Society of New Jersey, Section on Gastroenterology, held in Atlantic City. Dr. Harold S. Davidson, F.A.C.P., Atlantic City, led a discussion on this paper.

Dr. Fred M. Meixner, F.A.C.P., Peoria, Ill., has been reëlected President of the Illinois Tuberculosis Association and elected a member of the Board of Governors of the Mississippi Valley Conference on Tuberculosis.

On May 19, 1942, Dr. Meixner presented a paper entitled "The Tuberculous Obstetric Patient," at the meeting of the Illinois Medical Society in Springfield.

The 15th Graduate Fortnight of the New York Academy of Medicine will be held October 12–23, 1942. The subject of this Fortnight will be "Disorders of the Nervous System," and the program will include morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations. Among the Fellows of the College who will participate in the evening lectures at this meeting will be:

Dr. Edward A. Strecker, Philadelphia, Pa.—"Military Psychiatry";
Dr. Harold G. Wolff, New York, N. Y.—"The Emotions and Disease";
Dr. Walter Freeman, Washington, D. C.—"Prefrontal Lobotomy."

Dr. Robert Lyle Motley, F.A.C.P., Memphis, Tenn., was one of the guest speakers at the Fifth Councilor District meeting of the Arkansas Medical Society held recently in El Dorado. Dr. Motley spoke on "Diagnosis of Digestive Disturbances and Their Physiologic Explanation."

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., spoke on "Diseases of the Heart Amenable to Surgical Treatment" at the annual meeting of the California Medical Association held in Del Monte, May 4–7, 1942.

At a joint clinical conference of the Missouri and Illinois Post-Graduate Committees held in Belleville, Ill., April 9, 1942, Dr. Francis J. Braceland, F.A.C.P., Chicago, Ill., spoke on "Psychiatry—Recognition of the Psychopathic State in the Selectee."

The Medical and Chirurgical Faculty of the State of Maryland held its 144th Annual Meeting in Baltimore, April 28–29, 1942. Among the speakers on the program were:

Dr. Thomas Nelson Carey, F.A.C.P., Baltimore, Md.—"Rocky Mountain Spotted Fever";
Dr. Thomas P. Sprunt, F.A.C.P., Baltimore, Md.—"Blood Plasma Proteins";

Leon A. Fox, F.A.C.P., Colonel, (MC), U. S. Army—"The Doctor in War."

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., delivered one of the Trimble Lectures on "Syndromes Associated with Leukopenia."

Among the guest speakers at the 74th Annual Meeting of the Nebraska State Medical Association held in Omaha, May 4–7, 1942, were:

Dr. Henry W. F. Woltman, F.A.C.P., Rochester, Minn.—"Postoperative Neurologic Complications";

Dr. Benjamin Goldberg, F.A.C.P., Chicago, Ill.—"The Present Day Tuberculosis Problem";

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.—"Bedside Neurology for the General Practitioner";

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Endocrine Problems in the Male."

The South Dakota State Medical Association held its 61st Annual Meeting in Sioux Falls, May 13–15, 1942. At this meeting Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., spoke on "The Treatment of the Patient Over Fifty," and Dr. Herbert Z. Giffin, F.A.C.P., Rochester, Minn., discussed "Iron, Liver Extract and Vitamins in the Treatment of Various Types of Anemia."

Under the Presidency of Dr. Neil D. Buie, F.A.C.P., Marlin, Tex., the State Medical Association of Texas held its 76th Annual Session in Houston, May 11–14, 1942. Among the guest speakers were:

Leonard G. Rowntree, F.A.C.P., Colonel, (MRC), U. S. Army—"Medical Aspects of Selective Service";

Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.—"Diagnosis of Deficiency Diseases";

Dr. John H. Musser, F.A.C.P., New Orleans, La.—"The Heart that Grows Old."

Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., spoke on "Tuberculosis—The General Practitioner's Problem" at a meeting of the King County (Wash.) Medical Society at Seattle, March 16, 1942.

Dr. George W. McCoy, F.A.C.P., New Orleans, La., spoke on "Tropical Medicine: Scope and Achievements," and Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La., spoke on "The Story of Leprosy in the United States," at a symposium on Tropical Medicine conducted at the annual meeting of the Medical Library Association in New Orleans, May 7–9, 1942.

The American Association of the History of Medicine held its 18th Annual Session in Atlantic City, N. J., May 3–5, 1942, under the Presidency of Dr. Jabez H. Elliott, F.A.C.P., Toronto, Ont., Canada. Among the speakers at this meeting were:

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill.—"Théophile Bonet";

Dr. Maurice S. Jacobs, F.A.C.P., Philadelphia, Pa.—"Thomas Beddoes and His Contribution to the Treatment of Tuberculosis."

At the dinner meeting, May 4, Dr. Elliott delivered the presidential address on "Observation and Interpretation."

Under the Presidency of Dr. James H. Means, F.A.C.P., Boston, Mass., the Association of American Physicians held its 57th Annual Meeting in Atlantic City, N. J., May 5–6, 1942. Among the speakers were:

Dr. Harold W. Jones, F.A.C.P., Dr. Leandro M. Tocantins (Associate), and Dr. Lowell A. Erf (Associate), Philadelphia, Pa.—"Concentrated Blood Plasma, Intrasternally, in the Treatment of Shock";

Dr. Ralph A. Kinsella, F.A.C.P., St. Louis, Mo.—"Hyposthenia";

Dr. Roy W. Scott, F.A.C.P., and Dr. Curtis F. Garvin (Associate), Cleveland, Ohio—"Unusual Cardiac Mechanism Associated with Metastatic Cancer Involving the Left Auricle";

Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.—"Chorionic Gonadotropin: A Potent Stimulator of Growth."

Dr. Edwin E. Osgood, F.A.C.P., Portland, Ore., discussed "The General Principles of Chemotherapy" at the 106th Semi-annual Meeting of the Southern California Medical Association held in Riverside, April 10–11, 1942.

The Annual Alumni Clinic Day of Wayne University College of Medicine, Detroit, Mich., was observed May 6, 1942. Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., spoke on "Proved Preparations in Endocrine Therapy and Their Application," and Dr. John T. Murphy, F.A.C.P., Toledo, Ohio, spoke on "X-Ray Treatment of Lesions of the Face."

The New Hampshire Medical Society held its 151st Annual Session in Manchester, May 12–13, 1942. Dr. Paul D. White, F.A.C.P., Boston, Mass., conducted a symposium on "Heart Disease," and round table conferences were conducted by Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., on "Aspiration Pneumonia," and Dr. William Halsey Barker (Associate), Baltimore, Md., on "Recent Development in Therapy with Sulfonamide Drugs."

Dr. Irons also spoke at the Society's banquet. The subject of his address was "The Last Illness of Sir Joshua Reynolds."

On March 10, 1942, Dr. Reginald Fitz, F.A.C.P., Boston, Mass., spoke on "Clinical Aspects of Jaundice" at a meeting of the Broome County Medical Society at Binghamton, N. Y.

The 89th Annual Session of the Medical Society of the State of North Carolina was held in Charlotte, May 11–13, 1942. Among those who participated in the program were:

Dr. Paul D. White, F.A.C.P., Boston, Mass.—"Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease";

Henry C. Coburn, Jr., F.A.C.P., Brigadier General, (MC), U. S. Army—"The Responsibility of the Civilian Physician in the War Emergency";

Dr. Mark A. Griffin, F.A.C.P., Asheville, N. C.—"The Treatment of Chronic Alcoholism";

Dr. Archibald A. Barron, F.A.C.P., Charlotte, N. C.—"Experience and Treatment of Certain Mental and Nervous Disorders by Prefrontal Lobotomy."

Dr. Walter R. Johnson, F.A.C.P., Asheville, N. C., was awarded the Moore County Medal for the best paper read at the Society's 1941 Session. The subject of this paper was "Is Diverticulitis of the Colon a Surgical Disease?"

Dr. Benjamin E. Clarke, F.A.C.P., Providence, R. I., spoke on "The Blood Bank—A General Discussion" at a recent meeting of the Rhode Island Society of Pathologists in Woonsocket.

At a recent meeting of the Medical Society of Humacao (P. R.) County, a symposium on "Consideration of Injuries and Disabilities in Connection with Hostile Aircraft Attacks on Civilian Population" was conducted. Among the speakers were: Drs. Luis Manuel Morales, F.A.C.P., Juan A. Pons, F.A.C.P., Ramon M. Suarez, F.A.C.P., and Federico Hernandez Morales (Associate), all of San Juan.

Dr. Paul D. White, F.A.C.P., Boston, Mass., was elected President of the American Heart Association at its recent meeting in New York, N. Y. Among the other officers of the Association are: Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio, Vice President; Dr. T. Homer Coffen, F.A.C.P., Portland, Ore., Treasurer; and Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio, Secretary.

Dr. Jerome E. Andes, F.A.C.P., Tucson, Ariz. was one of the speakers at the recent annual meeting of the Arizona Public Health Association. Dr. Andes spoke on "Chemical Substances Occasionally Introduced into Food by Accident."

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, N. Y., spoke on "What to Do with Tuberculosis Discovered by Case Finding" and "Features of the Early Pulmonary Infiltration," at the annual session of the California Tuberculosis Association held in Los Angeles, April 9–11, 1942. Dr. Henry C. Sweany, F.A.C.P., Chicago, Ill., spoke on "Applications of Our Knowledge of Pathogenesis of Tuberculosis to Case Finding."

Among the guest speakers at the 83rd Annual Session of the Kansas Medical Society held in Wichita, May 11–14, 1942, were:

Dr. Alan Brown, F.A.C.P., Toronto, Ont., Canada—"Feeding Difficulties Encountered in the Newborn Period";

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa.—"Modern Therapy in Cardiology";

Dr. Paul A. O'Leary, F.A.C.P., Rochester, Minn.—"Modern Treatment of Syphilis";

Dr. Cyril M. MacBryde (Associate), St. Louis, Mo.—"Synthetic Estrogens and Their Use."

Dr. Irvin R. Fox, F.A.C.P., Eugene, Ore., has been reappointed a member of the State Board of Medical Examiners.

Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., delivered the 8th Edwin A. Jarecki Lecture at the Jewish Hospital, Philadelphia, Pa., April 23, 1942. The subject of his address was "The Responsibility of Being a Diabetic."

Dr. Tinsley R. Harrison, F.A.C.P., Winston-Salem, N. C., delivered the second annual J. Marion Sims Lecture on April 17, 1942, at the Medical College of the State of South Carolina in Charleston. The subject of his address was "Cardiac Dyspnea."

Dr. Orval N. Bryan, F.A.C.P., Nashville, Tenn., has been chosen President-Elect of the Tennessee State Medical Association at its annual meeting in Memphis, April 16, 1942.

At the recent meeting of the Kentucky Psychiatric Association, Dr. William K. Keller (Associate), Louisville, was installed as President.

Dr. J. Howard Holbrook, F.A.C.P., Hamilton, Ont., Canada, was recently presented with the city's Outstanding Citizenship Medal for 1941. The award was given Dr. Holbrook for his efforts over a period of thirty years to cut the death rate from tuberculosis in the city.

At the annual meeting of the North Dakota State Medical Association held in Jamestown, May 18–20, 1942, Dr. Gordon R. Kamman, F.A.C.P., St. Paul, Minn., spoke on "The Depressed Patient."

At the meeting of the Texas State Heart Association on May 11, 1942, the following officers were elected: President, Dr. Marvin L. Graves, F.A.C.P., Houston; Vice-President, Dr. P. B. Whitten, F.A.C.P., Dallas; Secretary-Treasurer, Dr. W. B. Whiting, F.A.C.P., Wichita Falls.

New Evans Memorial Building, Massachusetts Memorial Hospitals

On National Hospital Day, May 12, 1942, the new building of the Robert Dawson Evans Memorial in Boston was opened for inspection and occupancy. The Evans Memorial for Clinical Research and Preventive Medicine was originally dedicated on May 6, 1912, and throughout ensuing years it became necessary to expand the facilities. Accordingly, in 1940 Boston University purchased the old Robert Dawson Evans Memorial building on East Concord Street in Boston in order that they might expand their preclinical laboratories, and the Trustees of the Massachusetts Memorial Hospitals decided to construct the new Evans Memorial Building on East Newton Street immediately adjoining the Robinson and Collamore Buildings.

The new building contains nine floors and provides service for the group of Hospitals, such as the kitchens, dining rooms, admitting, bookkeeping and business offices, as well as the wards and laboratories of the Evans Memorial.

Dr. Chester S. Keefer, F.A.C.P., is the Director. The Department of Electrocardiography and Cardiology is under the supervision of Dr. James M. Faulkner, F.A.C.P. There will be laboratories for gastro-enterology, chemical laboratories for

investigation, a Department of Obstetrics, a Division of Bacteriology and Immunology, an Allergy Clinic, a Division of Pathology, et cetera.

Aside from the research activities of the various members of the Robert Dawson Evans Memorial staff, they will take an active part in the teaching of medical students of Boston University School of Medicine.

"It will be the constant purpose and objective of the Memorial to carry forward work in clinical research as set forth by the donor; that is to say, the investigation of the cause, prevention and treatment of disease." The inscription above the entrance of the original Memorial Building is "Truth above everything."

Grants-in-Aid Available through the Nutrition Foundation

The Nutrition Foundation, Inc., was organized December 21, 1941, to develop and support a comprehensive research and educational program in the science of nutrition. A part of the program has been planned to deal with nutrition in its immediate relation to public health. Another part of the program will be concerned with long-time studies of a more fundamental nature—the kind of exploratory research that should lay the foundation for better health and scientific guidance in the food industry of tomorrow.

The present war emergency makes it advisable to direct a fairly large part of the Foundation's activities into this field. The advice of Government agencies will be sought in relation to war emergency grants. Many of the members of its Scientific Advisory Committee are already on committees working with the National Research Council.

The Foundation does not plan to establish separate research laboratories, but instead will make its funds available to established institutions, such as universities with strong graduate divisions, where there are facilities for outstanding research work, and where the training of young people in the science of nutrition can be provided satisfactorily.

Application blanks for grants-in-aid may be obtained from the Executive Offices of the Foundation, Chrysler Building, New York City. Requests for grants will be submitted first to the Scientific Advisory Committee and then, if approved, to the Board of Trustees. Dr. Karl T. Compton, President of Massachusetts Institute of Technology, is the Chairman of the Board of Trustees of the Foundation.

OBITUARY

DR. I. SETH HIRSCH

Dr. I. Seth Hirsch was born December 3, 1880, in New York, N. Y., and died on March 24, 1942, at Mount Sinai Hospital, after a brief illness.

Dr. Hirsch attended the College of the City of New York from 1895 to 1898 and received his M.D. degree from the Columbia University College of Physicians and Surgeons in 1902. Between 1904 and 1914 he was Radiologist at several hospitals, including Mount Sinai, Beth Israel, Lebanon, City and Joint Diseases. Between 1910 and 1926 he was Director of the Roentgenological Department of Bellevue and four allied Hospitals—Fordham, Harlem, Gouverneur, and Neponsit Beach. From 1914 to 1917 he was Professor of Roentgenology at the New York Post Graduate Medical School, and since 1933 was Professor of Radiology at the New York University College of Medicine. For many years Dr. Hirsch was Director of the Roentgenological Department of Beth Israel Hospital and a Roentgenological Consultant to the New York State Compensation Commission.

Dr. Hirsch served with the armed forces of the United States during World War I and in 1919 was commissioned a Major in the Medical Reserve Corps of the United States Army.

At Bellevue in 1923 Dr. Hirsch conducted an experiment in the use of roentgen-ray apparatus in cancer treatment which physicians termed one of the most noteworthy up to that time. He exposed a woman cancer patient to a roentgen-ray current of 250,000 volts for a total of fifty-six hours. It was the first time that such a high voltage had ever been used for so long a period. This experiment followed a year and a half of preparation by Dr. Hirsch.

One of Dr. Hirsch's avocations was sculpture. He founded the New York Physicians Art Club, which held annual exhibitions of plastic and graphic art executed by physicians and entered much of his own sculpture.

Dr. Hirsch was a Fellow of the New York Academy of Medicine, the American Editors Association, the British Roentgen Society, the German Roentgen Society, member and a former Vice President of the Radiological Society of North America. He was a Fellow of the American Medical Association, member of the New York State and County Societies, a Fellow of the American College of Physicians since 1920.

In 1939, one-hundred and fifty friends, former students and colleagues honored Dr. Hirsch at a testimonial dinner and published a volume in his honor, entitled "Contributions to Radiology," which contained forty-five scientific articles. Dr. Hirsch also received an oil portrait of himself which had hung in the New York University College of Medicine and later was transferred to his home in New York.

Among the honors which came to Dr. Hirsch were a diploma in radiology from Cambridge University, in England, and honorary membership in Alpha Omega Alpha, honorary medical fraternity.

Dr. Hirsch practiced medicine in New York City for forty years, and was the author of "Principles and Practices of Roentgen Technique" and "Principles and Practices of Roentgen Therapy." He had written extensively on his specialty and had two books in preparation at the time of his death. He had also served as Associate Editor and Director of the Department of Technique and New Services of the American Journal of Electrology and Radiology.

Dr. Hirsch leaves a widow, two sisters, and four brothers, all of New York City.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

Hospital copy
Return to medical
To Brief

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